UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE PFIZER INC. SECURITIES LITIGATION

No. 04-cv-9866 (LTS) (DFE)

PFIZER DEFENDANTS' REPLY MEMORANDUM OF LAW IN SUPPORT OF THEIR MOTION TO EXCLUDE CERTAIN PLAINTIFFS' EXPERTS' OPINIONS REGARDING CELEBREX AND BEXTRA

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Defendants submit this reply memorandum of law in support of their motion to exclude the testimony of Plaintiffs' experts that prior to December 16, 2004, there existed reliable scientific evidence that Celebrex and/or Bextra was associated with a statistically significant increase in the risk of heart attacks and strokes.

PRELIMINARY STATEMENT

In its opening brief, Pfizer demonstrated that Plaintiffs' experts failed to satisfy *Daubert*'s standard for admissibility because their opinions are not based on reliable, objective methodologies. Rather, their opinions are the product of applying whatever methods would achieve their preferred outcome while ignoring conventional analytical techniques. Outside of litigation, Plaintiffs' own experts, in published articles and elsewhere, repeatedly have relied on appropriate and accepted methodologies for analyzing clinical study data, and their disregard of such methodologies here renders their opinions unreliable and inadmissible.

Plaintiffs' experts have manipulated the data in multiple ways. For instance, Plaintiffs' experts do not analyze the totality of the evidence, as conventional methodologies dictate. Instead, Plaintiffs' experts rely only on discrete pieces of Celebrex data in order to conclude that the Celebrex evidence established an increased heart attack and stroke risk before December 2004. Plaintiffs' experts ignore significant numbers of the available placebo-controlled trials, the vast majority of trials comparing Celebrex to NSAIDs like Motrin and Aleve, and voluminous observational studies showing that arthritis patients taking Celebrex have no greater risk of a heart attack or stroke than patients taking Motrin, Aleve or no medication at all. By relying on selected excerpts from the available data, what Plaintiffs' experts have done is no different than evaluating a baseball player's batting average based on two games out of a whole season or declaring the winner of an election based on limited reports from a few precincts out of hundreds casting votes.

If Plaintiffs' experts had considered the totality of Celebrex data, it would show that APC – an experimental, cancer prevention study in patients taking very high doses of Celebrex every day for years – is the only Celebrex clinical trial showing a statistically significant difference in

the occurrence of heart attacks and strokes. This study was not available until mid-December 2004 and was disclosed immediately to the public. In fact, the U.S. Food & Drug Administration ("FDA"), Judge Breyer, Justice Kornreich, and Plaintiffs' own experts, such as Dr. Joel Bennett – the only licensed doctor and prescriber of medication in Plaintiffs' affirmative case – found that APC provides the first evidence of a possible increased risk of heart attack and stroke related to Celebrex, at least in some patients, at some dose, after years of daily use. Moreover, as of 2009, several other equally large, high-dose, experimental, disease prevention studies have compared patients taking Celebrex to patients taking placebo, and not one has replicated the statistically significant difference seen in APC.

Further, outside of litigation, the FDA and the worldwide medical community also have compared the cardiovascular health of patients taking Celebrex to those taking Motrin and Aleve, and not a single researcher has found that any dose of Celebrex is any less safe for the heart than common doses of these household pain medications. Similarly, at the most commonly used doses of Celebrex, researchers have studied the cardiovascular health of millions of Celebrex patients, and to this day there remains no reliable evidence that arthritis patients taking Celebrex at typical doses are at any greater risk of a heart attack or stroke than patients who try to endure their pain without medication. This is why Celebrex remains one of the world's most commonly prescribed pain medications, and why millions of patients continue to rely on it to treat their pain.

Recognizing that APC yields the only statistically significant difference in the occurrence of heart attacks and strokes, Plaintiffs' experts resort to manipulated methodologies that are intended to achieve their desired result. For example, Plaintiffs argue against the principle of statistical significance, thereby ignoring their own experts' views outside of litigation as well as the accepted methodology for evaluating whether a true causal effect exists. Alternatively, in order to achieve statistical significance, Plaintiffs' experts also improperly select composite endpoint definitions that have no relevance to an analysis of heart attack and stroke risk.

While Plaintiffs argue that statistical significance is not relevant when assessing drug safety outcomes, that simply is not the case here because heart attacks and strokes are very common in the general population of arthritis patients, even in the absence of exposure to a medication. As a result, it is universally accepted in the medical and scientific communities that statistical significance is required to help distinguish a potential heart attack and stroke effect of a medication from other well-known causes of these conditions. That is why, outside of litigation, the FDA, Plaintiffs' own experts, and researchers evaluating the heart attack and stroke effects of any NSAID or other medication have relied on conventional principles of statistical significance before reaching opinions about the presence of those effects. It also is why Plaintiffs now attempt to migrate well outside the domain of the NSAID cardiovascular literature to find examples where statistical significance is unnecessary. In the circumstances on which Plaintiffs rely, however, statistical significance is not essential because the adverse events in question have unique or signature features, and they rarely or never happen in the absence of exposure to the medication. Here, without principles of statistical significance to evaluate the presence of an increased heart attack or stroke risk, there would be no objective standards, uniform criteria, or measurable error rates upon which to evaluate the reliability of Plaintiffs' experts' "trend" and "signal" methodologies. Such subjective, unverifiable methods are what *Daubert* was designed to exclude.

Alternatively, Plaintiffs' experts manipulate selective samples of the available data in an effort to contrive statistically significant differences in the occurrence of some post-hoc composite endpoints, though not ones that measure the risk of heart attacks and strokes. According to the FDA, APC was the only Celebrex clinical trial that supported the FDA's recommendation for a boxed label, which in turn relates to heart attacks and strokes (though the FDA was careful to highlight both the data contradicting the APC results and significant other data showing that arthritis patients taking typical doses of Celebrex have no greater risk of a heart attack or stroke than patients taking Motrin, Aleve, or no medicine at all). Now, in order to manufacture statistically significant differences, Plaintiffs' experts rely on composite endpoints

that neither measure heart attack and stroke risk nor bear any resemblance to the endpoints used by the FDA, the disinterested APC researchers, or Dr. Kearney, the author of the meta-analysis Plaintiffs' experts praise as the most reliable peer-reviewed meta-analysis to date.

Plaintiffs place significant reliance on a high-dose, experimental trial in 425 patients intended to evaluate whether Celebrex could attenuate the tragic progression of Alzheimer's disease (known as the "Alzheimer's 001" trial). In their post-hoc analysis of this trial, Plaintiffs experts rely on composite endpoint measures that include non-thrombotic events like palpitations, but at the same time exclude major thrombotic events such as stroke. Outside of litigation, no such endpoint ever has been used to evaluate the thrombotic safety of a medication, and Plaintiffs' own experts concede that their Alzheimer's 001 endpoints do not evaluate the heart attack or stroke risk of Celebrex. Because these endpoints do not measure heart attack and stroke risk, they are not relevant to Pfizer's *Daubert* challenge. Not surprisingly, Plaintiffs do not explain the relevance of an endpoint that does not to measure heart attack and stroke risk – *i.e.*, the risks that resulted in a boxed warning on the Celebrex label.

Plaintiffs also rely on Dr. Madigan's meta-analysis, which suffers from the same post-hoc endpoint manipulations as Plaintiffs' Alzheimer's 001 analysis, but many more methodological problems as well. For example, in addition to gerrymandering endpoint definitions that neither measure heart attack risk nor include the occurrence of stroke, Madigan ignored nearly a third of the available placebo controlled data. Madigan also employed an unreliable data collection process, which never has been utilized outside of litigation. In fact, while Plaintiffs' opposition concedes that Madigan missed certain events in his review of the Celebrex database, Plaintiffs only scratched the surface of mistakes related to Madigan's incomplete extraction of events from the database. In reality, Madigan failed to extract and to collect at least eight out of the 79 deaths that occurred in his incomplete set of trials. With respect to non-fatal events reviewed by Madigan, it is impossible to inventory the events he failed to collect because the entire process is undocumented and Dr. Baruch – the cardiologist Plaintiffs relied on to help collect the relevant non-fatal events – has no recollection of the process.

To compound these failings, Plaintiffs kept Madigan in the dark while they swapped Baruch's original cause of death determinations with those of Dr. Furberg – a non-cardiologist who has not diagnosed a patient's medical condition in decades and who is unable to describe the current diagnostic criteria for a heart attack. Furberg's new event counts cut against Celebrex, enabling Madigan to contrive a statistically significant difference in the occurrence of adverse events that fit his composite endpoint measures of something other than heart attacks and strokes. These new changes were done even though Madigan had no methodological concerns about Baruch's original event counts. Moreover, Plaintiffs' counsel did not give Furberg any diagnostic criteria to guide his cause of death determinations, so Furberg made up his own criteria. Unbeknownst to Madigan, Furberg also altered the endpoint definitions that were the basis of Madigan's analysis. Moreover, Furberg's cause of death determinations were based solely on one-line snippets of information, even though more detailed patient information was available. Furberg conceded that, outside of litigation, he had never employed such a process. He also conceded that a proper methodology would have been to reconcile the discrepancies between his counts and those of Baruch. Plaintiffs did not do that, however, and instead chose to proceed only with Furberg's counts.

Plaintiffs' experts' analysis of Bextra fares no better. Plaintiffs' experts ignore that the FDA recommended withdrawal of Bextra because of an increased risk of severe skin reactions compared to other NSAIDs. Here, too, both the FDA and the worldwide medical community rigorously studied the cardiovascular safety of Bextra and universally found no evidence that patients taking Bextra pills for approved doses were at any greater risk of a heart attack or stroke than patients taking Motrin, Aleve or no arthritis medication at all.

Rather than comparing the heart attack and stroke rates of Bextra patients to those taking Aleve or no arthritis medication at all, Plaintiffs' experts ignore the available arthritis data, and instead rely on the experimental, high-dose, heart bypass surgery trials ("the CABG trials") related to parecoxib, an experimental, intravenous form of Bextra that, in part, was not approved by the FDA because of unique clinical effects (*e.g.*, unsafe decreases in blood pressure) not seen

with arthritis uses of Bextra pills. In relying on parecoxib as a surrogate for Bextra, Plaintiffs' experts ignore the unique clinical effects of parecoxib, basing their opinions on an assumption rather than a methodologically proper analysis. Outside of litigation, Furberg has found that intravenous forms of a medication can cause adverse effects not seen with oral forms of the same medication – even where the different forms have comparable molecular structures. Here, none of Plaintiffs' experts separately analyzed the available parecoxib data or attempted to explain why cardiovascular effects such as blood pressure are different with parecoxib. A methodology is not reliable if it considers only the pieces of data that appear to support a hypothesis, but deliberately fails to address additional data that undercuts the hypothesis. Moreover, Bennett, the only expert in Plaintiffs' affirmative case who professes to understand how these medications work in the body, readily admits that the physiology of CABG patients is so unique that it is unreliable to apply the results of the CABG trials to arthritis patients. Because Plaintiffs' experts have no reliable method to establish that use of approved Bextra pills increases the risk of heart attacks and strokes, the Court should exclude any opinion that oral Bextra, the medication at issue here, increases the risk of heart attacks and strokes.

ARGUMENT

I. STATISTICAL SIGNIFICANCE IS ESSENTIAL FOR REACHING RELIABLE CONCLUSIONS ABOUT THE RISKS OF COMMON ADVERSE EVENTS SUCH AS HEART ATTACKS AND STROKES

Plaintiffs spend much of their opposition attempting to downplay the importance of statistical significance, in part by claiming that drug safety decisions often are made on the basis of evidence that is not statistically significant. Yet Plaintiffs ignore a critical distinction between the adverse events at issue here – heart attacks and strokes, which are among the most common events in the general population – and those types of very rare events where statistical significance is less relevant, all of which almost never happen in the absence of exposure to a medication, or which leave signature injuries that can be linked to the medication itself. Where,

as here, an event occurs frequently in the general population,[1] the medical and scientific communities rely on statistical significance to assess whether events occurring in patients taking a study medication are associated with the medication rather than due to background risk factors (*e.g.*, high cholesterol, high blood pressure, smoking) unrelated to the medication. That is why every peer-reviewed analysis written about the cardiovascular safety of NSAIDs relies on conventional statistical significance thresholds to evaluate the reliability of the published results.

Without statistical significance as the objective, established criteria to evaluate the probability that a numerical imbalance is due to the play of chance, researchers would have no way to test the reliability of their determinations. In other words, there would be no known error rate, a key indicator of admissibility under *Daubert*. Instead, as Plaintiffs' experts do here, the researchers would have to rely on standardless, hindsight-based approaches that cannot be validated or controlled for the rate of error. Such an approach is untenable as a matter of both science and the rules of evidence as articulated in *Daubert* and its progeny. In evaluating whether there was reliable evidence of an increased heart attack and stroke risk before December of 2004, the Court should reject Plaintiffs' attempts to evade the objective standards that statistical significance thresholds provide and that *Daubert* requires.

A. Statistical Significance Thresholds Are Used Universally by the Medical and Scientific Communities to Analyze Whether a Medication Increases the Risk of Heart Attacks and Strokes.

For common adverse events such as heart attacks and strokes, the medical and scientific communities use statistical significance thresholds to assess the safety of medications. Indeed, the FDA always requires statistically significant evidence when evaluating whether exposure to a medication is associated with injuries that occur frequently. Plaintiffs' experts recognize the

[1] Bennett testified that heart attacks are "the most common cause of [death] in Western society." Markel Decl., Ex. 3 at 73 (Bennett Dep., *In re Bextra*); *see* Markel Opp. Decl., Ex. 183 at 52 (Bennett Dep. [admitting heart attacks occur every day in patients never exposed to Celebrex or Bextra and that with common events like heart attacks and strokes, the only way to know if a real drug effect exists is to "do statistics"]). Bennett's deposition in this case did not occur until August 18, 2009, so that testimony was not available for Pfizer's opening brief.

importance of statistical significance in making reliable judgments about the link, if any, between exposure to a medication and events such as heart attacks and strokes. It is that need for an objective standard under *Daubert* that mandates the use of statistical significance here.

1. The FDA Requires Statistically Significant Evidence When Making Decisions About Events That Are Common in the General Population.

Statistical significance (expressed as *p*-values and/or confidence intervals) "permit an assessment of whether the results of a study are likely to represent a true association or random error." REF. MAN. at 354; *see also* Defs.' Br. at 16. Researchers also must examine the totality of the evidence, because results that are replicated in and consistent across studies give researchers confidence that observed differences are real. *See* Markel Decl., Ex. 3 at 76, 204, 379 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 8 at 62-63 (Furberg Dep.). Indeed, whether results are reproducible is a key hallmark of reliability. *See* REF. MAN. at 102.

Because of the importance of statistical significance in evaluating common events such as heart attacks and strokes, the FDA and the rest of the scientific and medical communities always have relied on statistical significance when assessing the cardiovascular safety of NSAIDs.[2] Indeed, Plaintiffs have not identified a single peer-reviewed study discussing the cardiovascular safety of NSAIDs that did not discuss the statistical significance of the results. Similarly, Judge Breyer and Justice Kornreich relied heavily on statistical significance in their assessment of the evidence in the product liability cases. Both judges found no reliable evidence of an increased risk at the dose most commonly used by arthritis patients and held that APC was the only trial to demonstrate a statistically significant increase in thrombotic risk.[3]

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[2] *See, e.g.*, Markel Decl., 55 at 5 (FDA Decision Mem. [noting that the results of the Alzheimer's 001 study "did not demonstrate a significantly increased risk of serious adverse CV events"]); Markel Opp. Decl., Ex. 174 at 1303-04 (Kearney et al., BRIT. MED. J., 2006;332(7553):1302-08 ["Kearney"] [finding "no significant difference in the incidence of serious vascular event between" patients on selective COX-2 inhibitors versus traditional NSAIDs]); Markel Decl., 74 at 1638-39, Table 3 (McGettigan et al., JAMA 2006;296:1633-1644 ["McGettigan"] [finding no significant increase in risk associated with Celebrex]).

[3] *See In re Bextra & Celebrex Mktg. Sales Pracs. & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1181-83 (N.D. Cal. 2007) ("*In re Bextra I*"); *In re Bextra and Celebrex*, No. 762000/2006, 2008 N.Y. Misc. LEXIS 720 at *27-28, 32, 34 (Sup. Ct. New York County Jan. 7, 2008) ("*In re Bextra II*").

In fact, outside the context of NSAIDs, the FDA universally requires evidence of a statistically significant association between an adverse event and a medication where the alleged injury occurs commonly in the general population – such as heart attacks and strokes – such that it is difficult to determine whether an event may be due to background medical conditions rather than drug exposure (an injury known as a "Type A reaction"). It is only where an adverse event is idiosyncratic and rarely occurs in the absence of a medication (known as a "Type B reaction") that the FDA will make safety decisions without statistically significant evidence. *See* App., Fig. 13. For example, the FDA noted that there were two clinical trials and numerous observational studies in which Vioxx was associated with a statistically significant increase in thrombotic risk. *See* Markel Decl., Ex. 55 at 5 (FDA Decision Mem. [APPROVe and VIGOR trials]); *id.* at 7-8 (observational studies). Similarly, when the FDA required a boxed heart attack warning on the Avandia label, it did so on the basis of meta-analyses of clinical trials and observational studies that were statistically significant. *See* App., Fig. 13. By contrast, the FDA decided to withdraw Duract, an event cited by Furberg, due to a handful of signature, spontaneous liver failure events which do not occur in the absence of a medication. Here, the FDA made judgments about the risk of rare, idiosyncratic skin reactions with Bextra without requiring statistical significance, while relying on statistical significance to analyze heart attacks and strokes.[4]

2. Plaintiffs' Experts Concede the Importance of Statistical Significance in Assessing Whether Results Are Reliable.

Contrary to the arguments of Plaintiffs' counsel, their own experts recognize that a *p*-value functions as an error rate by indicating the probability that the observed difference will arise by chance alone if the trial is repeated.[5] Plaintiffs' experts also recognize the importance of

[4] *Compare* Markel Decl., Ex. 55 at 12 (FDA Decision Mem. [discussing rare but serious skin reactions with Bextra]) *with id.* at 17 (analyzing the statistical significance of thrombotic results from clinical trials and concluding that Bextra is no less safe for the heart than other NSAIDs); *see also* Markel Reply Decl., Ex. 204 at 1 (Bextra Label, Nov. 2004 [adding warning regarding severe skin reactions based on adverse event reports]).

[5] *See* Markel Decl., Ex. 4 at 335 (FUNDAMENTALS OF CLINICAL TRIALS); Markel Decl., Ex. 12 at 147 (Kronmal Dep.); Markel Decl., Ex. 2 at 6 (Kronmal Rep.); *see also* REF. MAN. at 357.

achieving statistical significance as a prerequisite for reaching reliable conclusions about the safety of a medication.[6] Moreover, Bennett, Plaintiffs' only expert who professes to know how these medications work in the body has opined that statistical significance is necessary but not sufficient to establish causality. *See* Markel Decl., Ex. 3 at 539-40 (Bennett Dep., *In re Bextra*). Indeed, an established error rate is one of the key indicators of a reliable methodology.[7]

Plaintiffs' reliance on "scientific significance" – a concept they attempt to distinguish from *statistical* significance – is not conventionally accepted and in fact is wholly unreliable. Although Plaintiffs attempt to distinguish the concepts, "***[a]n important objective measure of scientific significance is 'statistical significance,'*** which usually requires that there is no more than a 5 percent probability that the scientist's findings are the results of chance."[8]

3. Both *Daubert* and Securities Law Reflect the Importance of the Objective Standard Statistical Significance Provides.

The Second Circuit likewise requires that plaintiffs asserting federal securities law claims based on a failure to disclose adverse events allegedly associated with a medication must plead and prove that there was statistically significant evidence of a causal relationship between the medication and the alleged harm. In *Honeyman v. Hoyt (In re Carter-Wallace, Inc. Securities*

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[6] *See* Markel Opp. Decl., Ex. 183 at 54-55, 104-06 (Bennett Dep. [admitting he relies on statistically significant results]); Markel Decl., Ex. 8 at 142 (Furberg Dep. [describing statistical significance as objective criteria to determine if results are consistent]); *id.* at 134 ("[Statistical significance is] how we judge results. And we limit the role of chance by testing for significance. This is not a chance finding; this a real finding."); Markel Decl., Ex. 99 at 196 (Madigan Dep., *Grutka v. Pfizer* [stating that statistical significance is "very useful to know what is the probability that the difference that you're seeing could have occurred by chance alone"]); Markel Decl., Ex. 13 at 136-37 (Madigan Dep. [expressing "uncertainty" with a p-value of 0.07]); *id.* at 158 (admitting his conclusions about Celebrex would be less convincing without statistical significance).

[7] *See Daubert v. Merrill Dow Pharms.*, 509 U.S. 579, 594 (1993); *Nimely v. City of N.Y.*, 414 F.3d 381, 396 (2d Cir. 2005) (holding that an established error rate is part of the "required indicia of scientific reliability"); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 475 (W.D. Pa. 2003) (rejecting an expert's methodology in part because "the error rate . . . is impossible to know or establish").

[8] Markel Reply Decl., Ex. 205 at 87 n.3 (Mark G. Haug, *Minimizing Uncertainty in Scientific Evidence* in SCIENTIFIC EVIDENCE REVIEW: CURRENT ISSUES AT THE CROSSROADS OF SCIENCE, TECHNOLOGY AND THE LAW (2006) (emphasis added) ["Haug"]). Plaintiffs also refer to the REFERENCE MANUAL ON SCIENTIFIC EVIDENCE and argue that statistical significance does not address the magnitude of the relative risk found, *see* Pls.' Opp. at 12, but it does reflect the *reliability* of the relative risk found in a study. Indeed, even where a result is statistically significant, that "does not mean that the result . . . is of significant or substantial magnitude." REF. MAN. at 354-55 n.55.

Litigation), 150 F.3d 153 (2d Cir. 1998) ("*Carter-Wallace I*"), the Second Circuit examined the question of whether a pharmaceutical company had a duty to disclose that it had received reports of certain adverse events purportedly related to a prescription medication. The court stated that:

> The statements in Carter-Wallace's Form 10-K and its "Report to Shareholders" did not become materially misleading until Carter-Wallace had information that Felbatol had caused a statistically significant number of aplastic-anemia deaths and therefore had reason to believe that the commercial viability of Felbatol was threatened. . . Drug companies need not disclose isolated reports of illnesses suffered by users of their drugs until those reports provide statistically significant evidence that the ill effects may be caused by – rather than randomly associated with – use of the drugs and are sufficiently serious and frequent to affect future earnings.[9]

The principle articulated in *Carter-Wallace I and II*, that standardless "trends" or "signals" are irrelevant because they do not establish that an adverse event is "caused by – rather than randomly associated with – use of the drug[]" in question, repeatedly has been affirmed by the Second Circuit as recently as August 2009. *See Masters v. GlaxoSmithKline*, 271 Fed. Appx. 46, 51 (2d Cir. 2008) (affirming dismissal of securities law complaint and stating that "harmful drug effects are immaterial – and thus need not be disclosed – unless those reports (1) show statistically significant evidence of an adverse effect, (2) establish that the adverse effect threatens the 'commercial viability' of the drug; and (3) show that the effect poses a significant risk to the company's future earnings"); *State Univs. Retirement Sys. of Ill. v. AstraZeneca PLC*, 2009 WL 1796534, at *2 (2d Cir. June 25, 2009) (citing *Carter-Wallace I*, affirming dismissal, and stating, "[w]e do not agree with the plaintiffs that the defendants were required to inform the public every time a participant in a study died, or even every time a death appeared perhaps to be related to the drug"); *Avon Pension Fund v. GlaxoSmithKline PLC*, 2009 WL 2591173, at *1 (2d Cir. Aug. 24, 2009) ("Reports or test results must yield reliable evidence of a drug's adverse

[9] *Id.* at 157; *see also Honeyman v. Hoyt (In re Carter-Wallace, Inc. Sec. Litig.)*, 220 F.3d 36, 42 (2d Cir. 2000) ("*Carter-Wallace II*") (affirming dismissal of securities law complaint based on failure to disclose adverse events associated with drug because "there was no statistical link between Felbatol and any adverse side effect before August 1, 1994," and "Carter-Wallace's awareness of medical reports that could have been random cannot lead to the conclusion that Carter-Wallace was reckless in permitting the advertisements to continue").

effects to give rise to a duty of manufacturers to disclose those results to potential investors. While the complaint conclusorily alleges that the results that the results of the meta-analyses 'showed an estimate' of an 'increased risk of heart attack,' . . . it pleads no facts indicating that the test results were even statistically significant.").[10] This rule also makes abundant sense, because requiring pharmaceutical companies to disclose the results of every clinical trial, even where such trials do not yield statistically significant evidence of a true causal effect, would "risk 'bury[ing] the shareholders in an avalanche of trivial information.'"[11]

Plaintiffs also assert that statistical significance is not a precondition to admissibility, *see* Pls.' Opp. at 51 & n.68, 55, but the handful of cases they cite either involved very rare, signature injuries, resulted in dismissal of plaintiffs' claims, or involved questions other than the reliability of an expert's opinion under *Daubert*.[12] In particular, Plaintiffs' citation to the *Seroquel* and *Neurontin* decisions are unavailing in that the experts there relied on statistically significant evidence *in addition to* non-significant evidence, or epidemiological evidence was not reasonably available.[13] Even if the cases Plaintiffs cite stood for the proposition that statistical

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[10] Indeed, Plaintiffs cite a few district court cases in an effort to mislead the Court into abandoning the Second Circuit's repeated insistence, reaffirmed only last month, that plaintiffs plead and prove statistical significance, *see* Pls.' Opp. at 49 n.66, but these decisions (which *granted* motions to dismiss because the statistically non-significant data at issue were not material) are inconsistent with the Second Circuit precedent cited above which is binding on this Court and compels Plaintiffs to demonstrate a statistically significant causal relationship.

[11] *Borochoff v. GlaxoSmithKline PLC*, 2008 WL 2073421, at *7 (S.D.N.Y. May 9, 2008) (*quoting San Leandro Emergency Med. Group Profit Sharing Plan v. Philip Morris Co.*, 75 F.3d 801, 810 (2d Cir. 1996)), *aff'd sub nom. Avon Pension Fund v. GlaxoSmithKline PLC*, 2009 WL 2591173 (2d Cir. Aug. 24, 2009) (Summary Order).

[12] *See Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1350, 1357 (6th Cir. 1992) (affirming summary judgment order in case involving rare birth defects), *cert. denied*, 506 U.S. 826 (1992); *Allen v. United States*, 588 F. Supp. 247, 258 (D. Utah 1984) (evaluating sufficiency of evidence, not *Daubert*); *In re Bendectin Prod. Liab. Litig.*, 732 F. Supp. 744, 748-49 (E.D. Mich. 1990) (evaluating summary judgment motion in case involving rare birth defects where plaintiffs had evidence other than non-significant epidemiological data); *Berry v. CSX Transp., Inc.*, 709 So. 2d 552, 554-57 (Fla. Dist. Ct. App. 1998) (evaluating rare toxic encephalopathy under *Frye* standard, in which the known error rate is irrelevant); *In re Joint E. & S. Dist. Asbestos Litig.*, 52 F.3d 1124, 1132 (2d Cir. 1995) (distinguishing a sufficiency of the evidence review and noting the case "is about sufficiency, not admissibility").

[13] *See In re Seroquel Prods. Liab. Litig.*, No. 6: 06-MD-1769, slip. op., at *22 (M.D. Fla. June 18, 2009) (agreeing that "the reliability of an expert's opinion should be seriously questioned, and perhaps even excluded altogether, when the expert can point to *no* evidence showing a statistically significant increased risk of disease"); *In re Neurontin Mktg., Sales Practices, & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 140-41 (D. Mass. 2009) (noting lack of reasonably available epidemiological data).

significance is not required for common injuries like heart attacks and strokes – which they do not – those cases run contrary to the great weight of authority under *Daubert*, which confirms that statistical significance "bears heavily on . . . reliability for evidential purposes."[14] Notably, Plaintiffs have not cited a single case in which a court abandoned the principles of statistical significance in interpreting *Daubert* in the context of heart attacks and stokes.

B. By Contrast, Plaintiffs' "Scientific Significance," "Signal," and "Trend" Methodologies Are Standardless, Subjective Approaches That Lack Critical Indicia of Reliability Under *Daubert.*

Even though statistical significance is the recognized, established, and reliable basis for assessing safety data for injuries such as heart attacks and strokes, Plaintiffs' experts base their opinions here on "trends" and "signals" and what they dub a "scientifically significant" risk – a concept that has no basis in the medical literature or case law. Their "scientific significance," "signal," and "trend" methodologies are not testable for reliability, are not based on objective criteria, and have no error rates. Therefore, they are not reliable methodologies, and any opinion based on them should be excluded. *See Daubert*, 509 U.S. at 593-95.

First, Plaintiffs' "scientific significance" standard is not testable. Plaintiffs' experts present no objective, identifiable way to determine when a study result is or is not "scientifically significant." Likewise, there are no tests to determine whether or when a "trend" or "signal"

[14] *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1057 (D.N.J. 1992) (citations omitted), *aff'd without opinion*, 6 F.3d 778 (3d Cir. 1993), *cert. denied*, 510 U.S. 1044 (1994); *see Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (affirming exclusion of opinions based on two studies that were not statistically significant); *Allen v. Penn. Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996) (rejecting data that is merely "suggestive" of a causal connection, but not statistically significant); *Smith v. Wyeth-Ayerst Labs. Co.*, 278 F. Supp. 2d 684, 691 (W.D.N.C. 2003) ("[E]pidemiological data cannot support an inference that a suspected risk factor caused an injury unless . . . the data is statistically significant under scientifically accepted statistical norms."); *Soldo*, 244 F. Supp. 2d at 533 ("Courts have emphasized that epidemiologic proof must be statistically significant."); *In re Norplant Contraceptive Prods. Liab. Litig.*, 215 F. Supp. 2d 795, 831 (E.D. Tex. 2002) ("[E]pidemiological data that is not 'statistically significant' cannot provide a scientific basis for an opinion on causation."); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1034 (S.D. Ill. 2001) (rejecting expert opinions based on "selective use of statistically insignificant data from epidemiological studies"); *Jones v. United States*, 933 F. Supp. 894, 898-900 (N.D. Cal. 1996) (finding that a reanalysis of statistically non-significant data to come up with a different conclusion is not "good science"); *DeLuca*, 791 F. Supp. at 1048-50, 1058-59 (rejecting plaintiff's experts' reanalysis of epidemiologic studies where original investigators found no statistically significant association); *Thomas v. Hoffman-LaRoche, Inc.*, 731 F. Supp. 224, 228 (N.D. Miss. 1989) (noting "total absence of any statistically significant study to assist the jury in its determination of the issue of causation").

constitutes a so-called safety concern. Indeed, in the context of heart attacks and strokes, Plaintiffs' experts do not know of any objective criteria for assessing whether or not a "trend" or "signal" exists because there are none – their analysis is completely subjective. *See* Markel Decl. Ex. 9 at 70, 244 (Furberg Dep.); Markel Opp. Decl., Ex. 183 at 49, 50-51 (Bennett Dep.).

Second, there are no known or potential error rates to assess whether the "trends," "signals," or "scientific significance" on which Plaintiffs' experts rely are reliable evidence of an association between Celebrex or Bextra and heart attacks and strokes. By contrast, when using statistical significance as the standard, one can calculate and measure the error rate (*e.g.*, with the widely accepted and conventional *p*-value of 0.05 representing a five percent chance that the result is not the true drug effect). *See* Markel Decl. Ex. 5 at 141 (EVALUATING CLINICAL RESEARCH). That is why statistical significance is "[a]n important objective measure of scientific significance . . ." Markel Reply Decl., Ex. 205 at 87 n.3 (Haug). Moreover, Plaintiffs' experts admit that "trends" are not reliable to assess whether a medicine increases or decreases risk, but are simply hints of potential issues that may require further study, because they are not based on statistically significant data. *See* Markel Opp. Decl., Ex. 183 at 55 (Bennett Dep.).

Third, Plaintiffs' "scientific significance" standard is not generally recognized in the published literature and is not generally accepted as a standard for assessing drug safety. For example, a search of published medical literature on PubMed.gov produces 202,837 articles that used the terms "statistical significance" or "statistically significant," whereas searches for the terms "scientific significance" or "scientifically significant" produce only 81 articles, none of which assess safety or risks associated with prescription medications, let alone their association with heart attacks and strokes. *See* Markel Reply Decl., Ex. 206 (Results of PubMed.gov Searches). Similarly, there are no accepted or published standards for assessing "trends" and "signals." *See* Markel Opp. Decl., Ex. 183 at 50 (Bennett Dep. [testifying that he is not "aware of any published standards regarding the interpretation of trends"]); Markel Decl., Ex. 8 at 70-71 (Furberg Dep. [testifying that he is "not aware of any objective criteria, either from Pfizer or the FDA or elsewhere" to decide whether a numerical imbalance constitutes a signal]).

Plaintiffs attempt to legitimize their reliance on "signals" and "trends" by pointing out that signals can suggest the need for further study. *See* Pls.' Opp. at 15. That, however, does not mean that a signal alone constitutes reliable evidence of an effect that can form the basis of a misrepresentation claim. Indeed, Plaintiffs admit that a safety signal "reflects *incomplete or insufficient* safety data necessary to determine whether the adverse trend is the result of chance or is drug-induced." Pls.' Opp. at 15 (citing Furberg Rep. at ¶ 28(e)) (emphasis added); *see also* Markel Opp. Decl., Ex. 183 at 55 (Bennett Dep. [testifying that "trends" are "a clue that perhaps one should pursue something"]). Because "trends" and "signals" are not reliable to establish a drug effect, they are "often wrong." *See* Markel Opp. Decl., Ex. 183 at 51 (Bennett Dep.). Indeed, as further illustration of the inherent lack of reliability in using "signals" and "trends" to detect true associations, Kronmal has gone so far as to say that one could label *any* imbalance in the number of events in a trial as a signal. *See* Markel, Decl. Ex. 12 at 186 (Kronmal Dep.).[15]

Plaintiffs further argue that the FDA does not require statistically significant evidence of risk when making drug safety decisions based on the public health. That ignores the distinction between Type A reactions (such as heart attacks and strokes, where the FDA *does* require statistical significance) and Type B reactions (such as the skin reactions seen with Bextra)

[15] Indeed, Furberg's "trend" and "signal" methodologies routinely lead to unreliable conclusions never validated by subsequent studies or accepted by the medical and scientific communities. Plaintiffs' opposition addresses a single instance involving calcium channel blockers ("CCBs"), while ignoring seven other instances Pfizer cited in which Furberg's claims were rejected by the medical and regulatory communities and never confirmed by further study. *See* Defs.' Br., App. 3. With respect to CCBs, Plaintiffs claim that Pfizer can point only to a "handful of newspaper and pharmaceutical trade articles" and brush off the criticisms as "heated rhetoric," Pls.' Opp. at 72, 74, when in fact criticisms of Furberg's methodologies were published in peer-reviewed scientific journals on many occasions, *including more than twenty such articles Pfizer cited*. *See* Defs.' Br., App., Fig. 3 (citing articles). Significantly, Plaintiffs also overlook entirely Furberg's pre-existing bias against Bextra and Celebrex, as two journals rejected Furberg's first iteration of his Bextra meta-analysis because he attempted to combine data from Bextra arthritis trials with the parecoxib CABG surgery trials, the FDA temporarily removed him from the Advisory Committee for intellectual bias and took no action in response to Furberg's criticisms of Pfizer's submissions to the Committee, and Furberg said he felt "vindicated" when Pfizer withdrew Bextra from the market. *Compare* Defs.' Br. at 56 *with* Pls.' Opp. at 68-72, 81. Plaintiffs also do not rebut that Furberg has a long history of testifying for plaintiffs in litigation against pharmaceutical manufacturers, which warrants heightened scrutiny from this Court. *See Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 435 (6th Cir. 2007); *Newton v. Roche Labs., Inc.*, 243 F. Supp. 2d 672, 679 (W.D. Tex. 2002). Finally, Furberg's testimony has been excluded in part in two recent cases in this Court. *See In re Fosamax Prods. Liab. Litig.*, No. 1:06-MD-1789 (JFK), 2009 WL 2222910 at *24-26 (S.D.N.Y July 27, 2009); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d. 531, 545-46, 549 (S.D.N.Y. 2004).

described above. *See* Section I.A.1 *supra*. Moreover, that the FDA may make precautionary public health decisions on the basis of a single statistically significant trial even where that trial was not replicated in other trials does not mean that non-significant data is sufficiently reliable to satisfy Plaintiffs' burden of proof in a court of law. Courts often hold that the standard of public safety on which the FDA bases its decisions is not applicable in the courtroom, law which Plaintiffs ignore entirely. *See* Defs.' Br. at 28 n.30 (citing cases). Plaintiffs' experts' use of "signals" and "trends" may be used in the context of public health and drug development decisions involving rare, signature injuries that generally do not occur without a drug exposure, but they have no place in a courtroom where common events such as heart attacks and strokes are at issue and where objective, reliable evidence is required.[16]

II. NO CELEBREX STUDY BEFORE APC SHOWED A STATISTICALLY SIGNIFICANT INCREASE IN THE RISK OF HEART ATTACKS AND STROKES

The totality of evidence today – from clinical trials, observational studies, and meta-analyses of clinical trials and observational studies – establishes that arthritis patients taking common doses of Celebrex are at no greater risk of heart attacks and strokes than those taking other NSAIDs like Motrin or Aleve or no medication at all. Only APC, an experimental study involving high doses of Celebrex taken for long periods of time to prevent colon cancer, has shown a statistically significant association, and that trial stands in stark contrast to other high-dose, long-term trials that showed no association. Faced with that totality of evidence, and recognizing that they should be held to principles of statistical significance, Plaintiffs attempt to manufacture statistically significant results by cherry-picking a pieced-together endpoint from the Alzheimer's 001 study that is not a reliable measure of thrombotic risk and relying on Madigan's incomplete and inaccurate meta-analysis.

[16] Plaintiffs also resort to the platitude that "absence of evidence is not evidence of absence," *see* Pls.' Opp. at 78, but the absence of reliable evidence means Plaintiffs cannot satisfy their burden to prove securities fraud. *See In re Bextra I*, 524 F. Supp. 2d at 1181 (noting that Plaintiffs cannot "satisfy their burden of proof based on a lack of evidence"); *Soldo*, 244 F. Supp. 2d at 558 (same).

A. The Totality of the Evidence Shows That Celebrex Is Safe in Real-World Arthritis Patients and Is No Less Safe for the Heart Than Motrin and Aleve.

Although Plaintiffs spend much of their brief trying to identify selective numerical imbalances in the Celebrex database of clinical trials, *see* Pls.' Opp. at 21-28, they do not dispute – because they cannot – that no Celebrex clinical trial before (or after) APC showed a statistically significant increase in the risk of heart attacks, strokes, or heart attacks and strokes combined (the "APTC" endpoint relied on by FDA, Kearney and many others), whether Celebrex was compared to placebo or other NSAIDs. *See* Defs.' Br. at 21.[17] Using an endpoint that is consistent with the current boxed label for all NSAIDs, the lack of statistical significance in any Celebrex trial is striking. *See* Defs.' Br., App., Figs. 4 & 5.

Plaintiffs also do not dispute that APC was the first and only trial to show a statistically significant increase in thrombotic risk and that APC was not replicated in other high-dose, long-term, experimental trials involving colon cancer (PreSAP and the Celecoxib/Selenium trial), Alzheimer's disease (ADAPT), breast cancer (the MA27 trial), and diabetic macular edema (the CDME trial), which the FDA recognized and Plaintiffs' experts admit.[18] Further, Plaintiffs do not refute that a well-respected meta-analysis of clinical trials – on which their own experts rely – does not show a statistically significant increase in the risk of heart attacks, strokes, or heart attacks and strokes combined, whether Celebrex is compared to placebo or other NSAIDs.[19]

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[17] Plaintiffs rely on the SUCCESS and CLASS studies to argue that there was evidence of a thrombotic risk with Celebrex prior to the APC trial, yet their own expert admits that neither of those trials showed a statistically significant increase in heart attacks and strokes, as the FDA and even Plaintiffs' counsel admit. *See* Markel Decl., Ex. 12 at 282-83 (Kronmal Dep.); Markel Decl., Ex. 55 at 5 (FDA Decision Mem.); Pls.' Opp. at 26-27.

[18] *See* Defs.' Br. at 23-24 & n.23, 27 & n.29; Markel Decl., Ex. 3 at 107 (Bennett Dep., *In re Bextra* [APC not replicated in ADAPT]); Markel Decl., Ex. 69 at 2107, Table 3 (Solomon S. et al., CIRCULATION 2008;117:2104-13 [Celecoxib/Selenium, MA27, and CDME trials]). Bennett makes these APC concessions as the only practicing physician in Plaintiffs' affirmative case, the only Plaintiffs' expert who professes to know how Celebrex and Bextra allegedly affect the body's clotting system, and as an author of the 2005 and 2007 AHA statements. *See* Markel Decl. Ex. 3 at 39, 41, 64, 615, 757, 821-22 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 9 at 3-5 (Bennett Rep.); *see generally* Markel Decl., Ex. 131 (Bennett et al., CIRCULATION 2005;111:1713-16 ["2005 AHA statement"]); Markel Decl., Ex. 73 (Antman et al., CIRCULATION, 2007;115:1634-42 ["2007 AHA statement"]).

[19] *See* Markel Opp. Decl., Ex. 174 at 1304 (Kearney); Markel Decl., Ex. 73 at 1635 (2007 AHA statement [citing Kearney]); *see also* Markel Decl., Ex. 182 at 135 (Caldwell et al., J. ROYAL SOC. MED. 2006;99:132-40 ["Caldwell"] [showing no statistically significant increase in risk for stroke, cardiovascular death, or a composite cardiovascular endpoint and showing a marginally significant result for heart attack alone only when including the

Similarly, Plaintiffs do not deny that observational studies of millions of real-world patients taking Celebrex as prescribed by their doctors show no increased risk for patients taking Celebrex compared to those taking another NSAID or no medication at all. *See* Defs.' Br. at 22 & n.18 (citing Graham and others). In particular, an undisputed and well-respected meta-analysis of observational studies involving 93,000 Celebrex patients found that patients who take Celebrex for its approved uses in real life have no greater risk of a thrombotic event than patients taking no NSAID at all or prescription Aleve, an NSAID that Plaintiffs' experts say is safe for the heart. *See* Defs.' Br. at 29 & n.33 (citing, *inter alia*, Markel Decl., Ex. 74 at 1638-39 [McGettigan]). Indeed, outside of litigation, Plaintiffs' experts rely on the McGettigan meta-analysis in evaluating the cardiovascular safety of NSAIDs. *See* Markel Decl., Ex. 73 at 1635, 1641 (2007 AHA Statement [citing McGettigan]); Markel Decl., Ex. 3 at 515-16, 572-73 (Bennett Dep., *In re Bextra*). Here, however, Plaintiffs' experts ignored the observational data altogether, which is all the more striking because they complain that the data they did consider lack power and the observational data that they ignore contain extraordinary amounts of statistical power. *See* Markel Decl., Ex. 12 at 138 (Kronmal Dep.).

On the basis of this data,[20] the FDA concluded that Celebrex is no less safe for the heart than other NSAIDs. *See* Markel Decl., Ex. 55 at 8, 10 (FDA Decision Mem.). Bennett agrees. *See* Markel Decl., Ex. 3 at 251-52 (Bennett Dep. *In re Bextra*). While Plaintiffs cite the boxed warning on Celebrex to support their claim that Celebrex increases the risk of heart attacks and strokes, *see* Pls.' Opp. at 76, their reliance on this warning is misplaced because the warning (which applies to *all* NSAIDs), states only that Celebrex "may" increase risk and is specific to

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APC data]); Markel Decl., Ex. 94 at 764-66 (Chen et al., PHARMACOEPIDEMIOL. DRUG SAF. 2007;16:762-72 ["Chen"] [finding no statistically significant increase in the risk of heart attacks alone for Celebrex compared to placebo or other NSAIDs]). Plaintiffs claim the Kearney meta-analysis "appears to indicate a statistically significant" risk of heart attack for Celebrex, Pls.' Opp. at 79 n.104, but the confidence interval crosses neutrality and is not statistically significant. *See* App., Fig. 14. Moreover, Kearney included data from APC, so such evidence would not have existed prior to December 16, 2004. *See* Markel Opp. Decl., Ex. 174 at Table 1, add'l materials online (Kearney).

[20] Contrary to Plaintiffs' assertions, *see* Pls.' Opp. at 37, Pfizer does not rely on its experts' conclusions in support of its motion. *See* Pfizer's Opp. to Pls.' Mot. to Exclude Dr. Wei at 14 n.9.

thrombotic events such as heart attacks *and strokes* – not the non-thrombotic endpoint Plaintiffs' use for Alzheimer's 001 or the endpoints Madigan uses to exclude the stroke event counts that favor Celebrex. *See* Defs.' Br. at 28; Markel Decl., Ex. 75 at 1 (Celebrex Label, Dec. 2006).[21]

If the evidence of an increased thrombotic risk for patients taking Celebrex compared to those taking no NSAID is at best weak, questionable, and limited today, it certainly did not exist before December 2004.[22] Faced with this totality of evidence, Plaintiffs contrive two pieces of so-called statistically significant evidence: (1) an endpoint from the Alzheimer's 001 study that does not measure the risk of heart attacks and strokes; and (2) Madigan's analysis, which manipulates endpoint definitions and event counts to achieve statistically significant results.[23]

B. Plaintiffs' Endpoint from the Alzheimer's 001 Study Is Irrelevant to the Issue of Thrombotic Risk.

1. When the Analysis Is Properly Limited to Thrombotic Events Such as Heart Attacks and Strokes, Alzheimer's 001 Does Not Show Increased Risk.

Plaintiffs argue that the high-dose Alzheimer's 001 study of a small number (450) of very old and sick patients "detected a material cardiovascular risk." *See* Pls.' Opp. at 23. The FDA

[21] Plaintiffs also cite the votes of the FDA Advisory Committee and determinations of other regulatory bodies to support their claim. *See* Pls.' Opp. at 28. Many of those determinations, however, applied only to selective COX-2 inhibitors as a whole, not to Celebrex in particular. *See* Jarvis 2d Decl., Ex. 47 at 5, 16 (Health Canada Comments, May 19, 2006 [discussing COX-2 inhibitors generally]); Jarvis 2d Decl., Ex. 58 at 1 (EMEA Q&A, Feb. 17, 2005 [reviewing COX-2 inhibitors as a class]). Moreover, the agency decisions were predicated on precautionary public health principles, not the level of proof a plaintiff must provide in a courtroom – a distinction Plaintiffs wholly ignore. *See* Defs. Mot. at 28 n.30. Finally, to the extent FDA and others made decisions relating to Celebrex specifically, those were based exclusively on the APC data. *See* Markel Decl., Ex. 55 at 9 (FDA Decision Mem.).

[22] Plaintiffs deny the importance of the courts' rulings in the product liability litigation, claiming that those courts held that there is a fact question as to whether Celebrex increases the risk of heart attacks and strokes at a daily dose of 400 mg. *See* Pls.' Opp. at 55-56. Plaintiffs are correct that the question before Judge Breyer and Justice Kornreich was different than that presented here, in that those courts appropriately evaluated the APC data because they had to assess, based on the totality of the evidence available today, whether Celebrex increased thrombotic risk. Here, however, the question is not whether the totality of evidence *today* demonstrates an increased risk, but whether there was reliable evidence as of December 16, 2004 – which means the APC data must be excluded.

[23] The unreliability of Plaintiffs' arguments is also demonstrated by what they allege is a 7-fold increase in risk, which no one in the world health community ever has claimed. The internal Pfizer analysis Plaintiffs cite also did not achieve statistical significance with respect to heart attacks, did not include stroke, and only achieved statistical significance by including events not relevant to thrombotic risk. *See* Jarvis 2d Decl., Ex. 1 at Cele IND 48395 00007988 (Table 12), Cele IND 48395 00007973 (Table 2).

and independent researchers studying the cardiovascular safety of Celebrex disagree. At the Advisory Committee meeting, Dr. James Witter of the FDA indicated that the Alzheimer's 001 results were "difficult to interpret . . . because of the small sample size which made relative risk and odds ratios unreliable." Markel Decl., Ex. 23 at 397-401 (Transcript of Arthritis Advisory Committee ["Ad. Comm. Tr."], Feb. 16, 2005 [noting further that "there don't appear to be any differences in [] the adverse events – deaths overall, cardiac deaths, serious adverse events – cardiovascular . . ."]). Plaintiffs' own experts Bennett and Kronmal agree.[24]

Dr. Witter also noted that Alzheimer's 001 "was conducted in a frail and fragile population that had substantial co-morbidities and concomitant medications, making it difficult to know how to generalize these results." Markel Decl., Ex. 23 at 398 (Ad. Comm. Tr., Feb. 16, 2005). He further observed that the Celebrex group in the study had baseline "imbalances in terms of hypertension, diabetes, those that had bypass surgery, those that had history of ischemia and those that had history of coronary-artery disease" as compared to the placebo group. *Id.*; *see also* Markel Decl., Ex. 58 at 36 (Presentation by Dr. James Witter, Feb. 16, 2005). In other words, the Celebrex group was materially sicker than the placebo group *before* either group took its first dose of study medication. Following the Advisory Committee Meeting, the FDA specifically found no statistically significant increase in the risk of thrombotic events in the Alzheimer's 001 trial. *See* Markel Decl., Ex. 55 at 5 (FDA Decision Mem. [stating the trial "did not demonstrate a significantly increased risk of serious adverse [cardiovascular] events"]). Plaintiffs' experts agree that the trial did not show a statistically significant increase in the risk of heart attacks, strokes, or the "APTC" endpoint of heart attacks and strokes combined.[25]

The FDA's determination was consistent with the conclusions of the investigators who conducted the trial, who noted that the results were driven not by thrombotic events such as heart

[24] *See* Markel Opp. Decl., Ex. 183 at 85 (Bennett Dep. [conceding it is "impossible" to interpret the heart attacks in the trial]); Markel Decl., Ex. 2 at 298 (Kronmal Dep. [admitting insufficient data to assess heart attack risk]).

[25] *See* Markel Opp. Decl., Ex. 183 at 79 (Bennett Dep.); Markel Decl., Ex. 8 at 162-63 (Furberg Dep.); Markel Decl., Ex. 12 at 294 (Kronmal Dep.); Markel Decl., Ex. 2 at 23 (Kronmal Rep.).

attacks and strokes, but instead by non-thrombotic events unrelated to Plaintiffs' proffered "imbalance" hypothesis and the public health debate related to all NSAIDs. *See* Markel Decl., Ex. 64 at 18-19 (Soininen at al., DEMENT. GERIATR. COGN. 2007;23:8-21 ["Soininen"] [noting that "[t]hese differences were primarily driven by the individual terms cardiac failure, fibrillation atrial, and angina pectoris"]). The FDA's judgment also was confirmed in the Kearney, Caldwell, and Chen meta-analyses cited and relied on at various times by Plaintiffs' experts[26] – each of whom used endpoints other than those selected by Plaintiffs and found no statistically significant increase in thrombotic risk in the Alzheimer's 001 trial. Indeed, the U.S. Securities & Exchange Commission ("SEC") investigated all disclosure issues related to Alzheimer's 001 and terminated its investigation without taking any action.[27] Finally, the NIH-sponsored ADAPT trial, a Celebrex trial that was independent, larger (2,528 patients), and in the same Alzheimer's population, showed no increased risk of thrombotic events, thus confirming the unreliability of any opinion that the Alzheimer's 001 data shows an increased risk of heart attack and stroke.[28]

2. Plaintiffs Rely on an Unprecedented Endpoint That Is Irrelevant to the Issue of Thrombotic Risk.

Because the Alzheimer's 001 trial did not show a statistically significant increased risk of heart attacks and strokes and was not replicated in the ADAPT trial – as the FDA and other researchers confirmed – Plaintiffs fashion their cardiovascular risk argument around Furberg's

[26] *See* Markel Decl., Ex. 60, at 1303 (Kearney) [using the APTC endpoint]; Markel Decl., Ex. 182, at 133 (Caldwell) [examining fatal or non-fatal MI (primary endpoint) and fatal or non fatal cerebrovascular events (thrombotic or hemorrhagic), cardiovascular mortality and the composite endpoint of serious cardiothromboembolic events (secondary endpoint)]; Markel Decl., Ex. 94, at 763 (Chen) [using the endpoint of fatal or non fatal heart attack]).

[27] *See* Markel Decl., Ex. 65 at 1 (Ltr. from SEC to Ethan Posner, Aug. 16, 2006). Plaintiffs also cite to the December 2004 letter from the co-chairs of the Alzheimer's 001 Data Safety Monitoring Board ("DSMB") regarding the results of the study in an attempt to bolster their argument that there was evidence of thrombotic risk before the APC study results were revealed and that Pfizer kept these data from the FDA. *See* Pls.' Opp. at 24-25. Yet FDA included and discussed the results of the Alzheimer's 001 trial in its review of all Celebrex studies during the February 2005 Advisory Committee Meeting and indicated that it was aware of the results well before that time. *See* Markel Decl., Ex. 23 at 398-401 (Ad. Comm. Tr., Feb. 16, 2005 ["*We were aware of this study.* This information had been discussed previously."] [emphasis added]).

[28] *See* Markel Decl., Ex. 54 at 0007 (ADAPT Research Group, PLOS CLIN. TRIALS 2006;1(7): e33); Markel Opp. Decl., Ex. 183 at 87-88 (Bennett Dep. [confirming ADAPT did not replicate Alzheimer's 001]).

hodgepodge endpoint consisting of various "heart related events."[29] Many of those "heart related events," such as pulmonary edema and atrial fibrillation, are not thrombotic in nature (*i.e.*, they are not associated with clot-related events such as heart attacks and strokes)[30] and thus bear no relation to the subject of the current boxed label, the cardiovascular endpoint relied on by the cardiovascular safety team in APC, Plaintiffs' own FitzGerald hypothesis, Plaintiffs' complaint, or the subject of Pfizer's motion here.[31]

Plaintiffs do not dispute that many of the cardiovascular events included in the Alzheimer's 001 endpoint Furberg selected are not used by the medical community to evaluate heart attack and stroke risk, that Furberg never has used such an endpoint in his career in clinical research, and that outside of litigation he has used the APTC endpoint to assess thrombotic risk. *Compare* Pls.' Opp. at 76 *with* Defs.' Br. at 57-59. Even more significantly, in his Bextra/parecoxib editorial, ***Furberg selected heart attacks and strokes as his composite endpoint*** to evaluate thrombotic risk in the CABG trials – but did not include any of the non-thrombotic events in his Alzheimer's 001 endpoint. *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249). Furberg also admits that heart attacks and stroke "go hand in hand." *See* Markel Decl., Ex. 7 at 397 (Furberg Dep., *Haslam v. Pfizer* [testifying he cannot distinguish Bextra's heart attack risk from its stroke risk]). Furberg relies on his arbitrary combination of events despite his own statements outside of litigation that "[p]ooled estimates relating to secondary hypotheses should only be considered if they have a clear pharmacological and biological foundation and even then should be interpreted conservatively." Markel Decl. Ex.

[29] *See* Pls.' Opp. at 24; Markel Decl., Ex. 1 at 18 (Furberg Rep. [including stroke, heart failure, pulmonary edema, myocardial infarction, angina pectoris, and atrial fibrillation]).

[30] *See* Markel Decl., Ex. 2 at 22-23 (Kronmal Rep. [focusing his analysis on heart attack and cardiovascular death]); Markel Decl., Ex. 161 at 240 (Baruch Dep. [testifying that atrial fibrillation is not a thrombotic event and that angina is generally non-thrombotic]); Markel Decl., 3 at 27-28 (Furberg Dep. [admitting that heart failure and angina are not induced by a clotting mechanism]); Markel Opp. Decl., Ex. 183 at 26 (Bennett Dep. [testifying that he would never include atrial fibrillation or heart failure in an endpoint to measure platelet effects]).

[31] *See* Markel Opp. Decl., Ex. 183 at 26 (Bennett Dep. ["If you think that a drug is causing thrombosis, then one measures – looks for heart attack and stroke, end points of thrombotic processes."]); *id.* at 86 (conceding Alzheimer's 001 endpoint says nothing about heart attacks); Markel Reply Decl., Ex. 207 at 27 (Compl.).

10 at 301 (Furberg & Morgan, STAT. MED. 1987;6:295-03); *see* Markel Decl., Ex. 8 at 80 (Furberg Dep. [claiming he dislikes any post hoc, composite endpoint]).

Furberg's endpoint manipulations also conflict with the endpoints used by independent researchers analyzing the cardiovascular safety of selective COX-2 inhibitors, or endorsed by Plaintiffs' other experts.[32] Indeed, Plaintiffs' only expert who professes to understand how NSAIDs work in the body rejects Furberg's unprecedented, kitchen-sink endpoint from the Alzheimer's 001 trial because it does not measure the risk of heart attacks. *See* Markel Opp. Decl., Ex. 183 at 26 (Bennett Dep. [testifying that he never would include atrial fibrillation or heart failure in an endpoint intended to measure a platelet effect as alleged here]).

Plaintiffs claim that Furberg's inclusion of events not associated with clots is appropriate because NSAIDs increase the risk of conditions such as hypertension. *See* Pls.' Opp. at 76. Yet Furberg conceded that the medical community has known for years that NSAIDs increase blood pressure, as did Bennett.[33] Bennett also conceded that Celebrex is *safer* than other NSAIDs in numerous other measures of cardiovascular safety. *See* Markel Opp. Decl., Ex. 183 at 222-23 (Bennett Dep. [discussing the lack of increased risk for peripheral edema, hypertension, renal dysfunction and arrhythmia with Celebrex in the Zhang meta-analysis, on which he and the other AHA authors relied]). Moreover, the risk of hypertension associated with all NSAIDs was disclosed in the Celebrex label when it was first introduced to the market. *See* Markel Decl., Ex. 24 at 11, 15, 17 (Celebrex Label, Jan. 1999). For that reason, it is not surprising that Plaintiffs' complaint is not – and could not be – focused on Pfizer's purported failure to disclose potential hypertension; rather, their complaint is predicated on an allegedly undisclosed risk of thrombotic

[32] *See* Markel Opp. Decl., Ex. 174 at 1303 (Kearney); Markel Decl., Ex. 94 at 763 (Chen); Markel Decl., Ex. 182 at 133 (Caldwell), Markel Decl. Ex. 97 at 4-5 (Madigan Rep.); Markel Decl., Ex. 12 at 244-45 (Kronmal Dep. [testifying that he would use a combined endpoint of MI and sudden cardiac death]).

[33] *See* Markel Decl., Ex. 8 at 184-86 (Furberg Dep. [testifying that NSAIDs' potential to increase blood pressure was brought to his attention almost a decade before COX-2s entered the market]); *id.* at 125 (conceding the connection between NSAIDs and heart failure was known in the medical community prior to the COX-2 entering the market); Markel Opp. Decl., Ex. 183 at 43-44 (Bennett Dep. [testifying that he and the medical community were aware that all NSAIDs have the potential to increase edema and hypertension for "10 or 20 years"]).

events such as heart attacks and strokes. *See, e.g.*, Markel Reply Decl., Ex. 207 at 25-26, 42, 48-49 (Compl.). Indeed, that is why Pfizer's motion is directed toward the risk of thrombotic events such as heart attacks and strokes – not all cardiovascular events of any kind.

Plaintiffs also contend that Furberg simply used the events reported by Pfizer, *see* Pls.' Opp. at 65-66, but that mischaracterizes the data on which his opinion is based. Furberg relied on tables Pfizer posted on a web site, which individually listed *all* adverse events reported in the study that occurred in more than one patient, and which were not designed to evaluate or to interpret the thrombotic data. *See* Markel Decl., Ex. 8 at 144-45, 147-48 (Furberg Dep.); Jarvis 2d Decl., Ex. 12 at 6 (PhRMA Posting); *see also* Markel Decl., Ex. 64 at 15-16 (Soininen [same]). Furberg chose a select number of those events to "add[] up," without providing any valid methodological, medical, or scientific basis for his endpoint other than that they related to the cardiovascular system. Markel Decl., Ex. 8 at 147-48 (Furberg Dep.). Instead of relying on one of Plaintiffs' three testifying statisticians, he then gave the numbers he "added up" to a graduate student to calculate a *p*-value. *See id.* In contrast, the Alzheimer's 001 investigators specifically analyzed thrombotic risk in a peer-reviewed publication, and did not rely on the results of the combination of events Furberg included in his endpoint definition. *See* Markel Decl., Ex. 64 at 15-16 (Soininen); *see also* Jarvis 2d Decl., Ex. 12 at 6 (PhRMA Posting).

In addition to using an inappropriate combined endpoint, Furberg ignored a material portion of the data associated with the Alzheimer's 001 study. For example, Furberg ignored data from extensions of the Alzheimer's 001 study, even though he was aware of those data. Markel Decl., Ex. 8 at 171 (Furberg Dep.). Consistent with the study authors, Bennett agreed that the extension of the Alzheimer's 001 study should be included in any statistical analysis of the data. *See* Markel Opp. Decl., Ex. 183 at 93 (Bennett Dep.). Thus, the Court should reject Furberg's attempt to use selective pieces of the Alzheimer's 001 data and an endpoint that bears no relation to the APTC endpoint, FDA's endpoint, the subject of the boxed label for all NSAIDs, or the opinions that Pfizer seeks to exclude.

C. Madigan's Meta-Analysis Is Based on a Flawed Collection Process and an Undocumented, Unprecedented Classification Procedure.

Plaintiffs also turn to Madigan's meta-analysis to create other evidence that achieves statistical significance. Yet Madigan chose unreliable endpoints, used incomplete data, and employed an undocumented and inaccurate classification and reclassification procedure never used outside of litigation. Accordingly, Madigan's meta-analysis is inadmissible under *Daubert.*

1. Madigan's Endpoints Do Not Address Heart Attacks and Strokes.

Madigan's endpoints were not used as a valid basis to evaluate the heart attack and stroke risks of NSAIDs before December 16, 2004.[34] Plaintiffs concede that Madigan's meta-analysis only reaches statistical significance before APC through his contrived "Hard CHD" endpoint (heart attack and sudden cardiac death, but not stroke), which he admits he never has used before and which no one other than Madigan ever has used to evaluate Celebrex, *see* Markel Decl., Ex. 13 at 230, 245, 255-57 (Madigan Dep.),[35] and his "myocardial thromboembolic" endpoint, which excludes stroke and lumps in heart attack with nearly a dozen other health outcomes. *See* Markel Decl., Ex. 97, at 4 (Madigan Rep.).[36] Moreover, while Plaintiffs defend Madigan's endpoint

[34] Plaintiffs contend that Pfizer did not challenge all four of Madigan's endpoints. Plaintiffs themselves concede that Madigan did not rely on two of his four endpoints in drawing his conclusions. *See* Pls.' Opp. at 62. Moreover, neither of Madigan's other two endpoints include stroke, and he identified his "Hard CHD" endpoint as his primary analysis – which is why Pfizer's motion focused on that endpoint. *See* Markel Decl., Ex. 97 at 4 (Madigan Rep.).

[35] Plaintiffs attempt to validate Madigan's "Hard CHD" endpoint by citing an article referenced in Madigan's report, but that article does not use Madigan's endpoint at all. *Compare* Markel Decl., Ex. 101 (Sever et al., LANCET 2003;361:1149-1158 [evaluating heart attacks and fatal coronary heart disease]) *with* Markel Decl., Ex. 97 at 4 (Madigan Rep. [evaluating heart attacks and *sudden* cardiac death]). Plaintiffs also suggest that a search of Google Scholar validates that endpoint. *See* Pls.' Opp. at 60. They offer nothing to document that statement, and a search of Google Scholar reveals that the term is used differently in the literature than by Madigan. *Compare* Jarvis 2d Decl., Ex. 107 at 1 (Google Scholar Search Results [heart attacks and cardiovascular death]) *with* Markel Decl., Ex. 97 at 4 (Madigan Rep. [heart attacks and *sudden* cardiac death]).

[36] Plaintiffs' opposition makes much of the fact that Madigan's "myocardial thromboembolic" endpoint was used by Pfizer in one of its submissions to the FDA and that it contained a purportedly statistically significant finding. *See* Pls.' Opp. at 1 n.2, 57 (citing Jarvis 2d Decl., Ex. 1). That composite endpoint contained a number of outcomes other than heart attack, however, and was one of dozens of combinations Pfizer studied. *See* Jarvis 2d Decl., Ex. 1 at 25-26, Table 5.1.2.4. Plaintiffs' citation to a finding of 4.84 relative risk for heart attacks at the 400 mg daily dose level for Celebrex is similarly unavailing, as that result was not statistically significant. *See id*. at 41.

selection on the basis of his purported collaboration with Baruch, Baruch could not recall any details of such a collaboration. *See* Markel Decl., Ex. 161 at 41-43 (Baruch Dep.).[37]

Notably, Madigan's exclusion of stroke from these two endpoints is inconsistent with Plaintiffs' "imbalance" hypothesis,[38] which posits that selective COX-2 inhibitors increase the risk of heart attacks *and stroke.* Moreover, the failure to include stroke puts Madigan at odds with: (1) Plaintiffs' other experts in this litigation, who include stroke in their analysis of the Bextra and Celebrex data generally[39] and the parecoxib CABG surgery trials in particular;[40] (2) Plaintiffs' experts outside this litigation, including Madigan's own Vioxx litigation analysis;[41] (3) FitzGerald, who, along with Furberg, included stroke in their Bextra/parecoxib editorial;[42] (4) the APC researchers and other independent scientists assessing the cardiovascular safety of NSAIDs;[43] and (5) most importantly, the FDA,[44] which chose the APTC endpoint – not

[37] Baruch also was not familiar with the "Hard CHD" endpoint, could not define it, and could not recall ever using that endpoint himself or even reading a published paper that used it. *See id.* at 43-44, 46-48.

[38] *See* Markel Opp. Decl., Ex. 183 at 26 (Bennett Dep. ["If you think that a drug is causing thrombosis, then one measures – looks for heart attack and stroke, end points of thrombotic processes."]); Markel Decl., Ex. 3 at 70-72 (Bennett Dep., *In re Bextra* [admitting that APTC is well-accepted and that he believes it to be a valid endpoint]); *see also* Markel Decl., Ex. 8 at 429 (Furberg Dep. [testifying that "you have to take into account the mechanism of action of the drug" in selecting endpoints]).

[39] For example, Plaintiffs' only cardiologist Baruch does not endorse the endpoints chosen by Furberg, Madigan, or Kronmal, but instead testified that he predominantly looks at heart attacks, strokes, and cardiovascular deaths – that is, the APTC endpoint – in his analysis of Bextra and Celebrex. *See* Markel Decl., Ex. 161 at 147 (Baruch Dep.); *see also* Markel Decl., Ex. 131 at 1715 (2005 AHA statement [discussing APTC endpoint and including risk of stroke in analysis]); Markel Decl., Ex. 73 at 1635, 1639, 1640 (2007 AHA statement [same]).

[40] *See* Markel Decl., Ex. 1 at 18 (Furberg Rep. [including stroke in his Alzheimer's 001 analysis]); Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249 [including stroke in his CABG meta-analysis]); Markel Decl., Ex. 82 at 1487-88 (Ott et al., J. THORAC. CARDIOVASC. SURG. 2003;125:1481-92 ["Ott"] [CABG-1 publication]); Markel Decl., Ex. 87 at 1081, 1087 (Nussmeier et al., N. ENGL. J. MED. 2005;352:1081-91 ["Nussmeier"] [CABG-2 publication]); Markel Decl., Ex. 9 at 10-11 (Bennett Rep. [citing Ott]); Markel Decl., Ex. 1 at 31, 41 (Furberg Rep. [referring to Ott and Nussmeier]); Markel Decl., Ex. 61 at 5 (Baruch Rep. [referring to Nussmeier]).

[41] *See* Markel Decl., Ex. 13 at 237-39 (Madigan Dep. [discussing how his choice of endpoint is this case was influenced by his previous Vioxx litigation analysis]); Defs.' Br., at 44, App., Fig. 1 (noting that in the Vioxx litigation, Madigan used a composite endpoint that included stroke to evaluate the cardiovascular safety of Vioxx); Defs.' Br. at 26 n.26, 68 (citing Plaintiffs' experts using the APTC endpoint outside of litigation).

[42] *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249).

[43] *See* Markel Decl., Ex. 49 (Solomon S. et al., N. ENGL. J. MED. 2005;352:1071-80 [endpoint including stroke]); Markel Opp. Decl., Ex. 174 at 1303 (Kearney [APTC endpoint]); Madigan Decl., Ex. 182 at 132 (Caldwell [stroke]).

any of Madigan's endpoints – to address the thrombotic risk that is currently the subject of the boxed warning for Celebrex and all other NSAIDs. Plaintiffs' own experts have acknowledged the impropriety that Madigan engaged in by switching endpoints from study to study to achieve a desired result.[45] Because Madigan's endpoints have no bearing on the heart attack and stroke concern at issue here, Madigan's meta-analysis has no relevance to key issues in this litigation.[46]

2. Due to Unreliable Data Collection Methods, Madigan Ignored Entire Studies and Missed Patient Events in the Trials He Did Consider.

Plaintiffs incorrectly represent that Madigan "analyzed all studies, regardless of duration, where study participants received at least 100 mg of Celebrex daily." Pls.' Opp. at 67. Because Madigan chose to review only clinical trials with electronic SAS data files, he ignored numerous studies – even though published literature and study reports with much more detail were available to him. *See* Defs.' Wei Opp. at 16 n.12 (listing dates and bates numbers of study reports with patient narratives). For example, Madigan failed to include the NIH-sponsored ADAPT study, even though that trial involved more thrombotic events than any other Celebrex trial – a fault that Plaintiffs' expert Bennett criticizes.[47] As a result of Madigan's failure to consider these other trials, his meta-analysis evaluates only approximately 70% of the cardiovascular events in placebo-controlled trials – which means he missed more than 40 events. *See* App., Fig. 15. Madigan also ignored data from any clinical trials comparing Celebrex to

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[44] The FDA chose the APTC endpoint to assess selective COX-2 inhibitors and all other NSAIDs because it is "a widely accepted endpoint in assessing the benefits and risks of a drug for [cardiovascular] outcomes." Markel Decl., Ex. 55 at 4 (FDA Decision Mem.).

[45] *See* Markel Decl., Ex. 12 at 228 (Kronmal Dep. ["[Y]ou can't do a meta-analysis where you use one endpoint for one study and another endpoint for another."]); Markel Decl., Ex. 5 at 42 (EVALUATING CLINICAL RESEARCH [warning that "[r]ed flags may include the use of unusual or illogical composites, e.g., outcome measures that have uncertain clinical relevance"]).

[46] *See Kuhmo Tire Co., Ltd v. Carmichael*, 526 U.S. 137, 141 (1999); *Daubert*, 509 U.S. at 589, 591; *United States v. Williams*, 506 F.3d 151, 160 (2d Cir. 2007); *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d at 540.

[47] Bennett has criticized meta-analyses that are based on an incomplete set of clinical trials. *See* Markel Decl., Ex. 3 at 306-07, 309 (Bennett Dep., *In re Bextra*). Specifically, Bennett believes it is appropriate to include ADAPT in a meta-analysis of Celebrex data, which Madigan failed to do. *See id.* at 297-98 (Bennett Dep., *In re Bextra*).

other NSAIDs[48] or from observational studies of real world patients. Madigan made these collection choices even though Plaintiffs' experts acknowledge that any drug safety analysis should consider the totality of the evidence.[49]

Even with regard to the studies that Madigan did consider, he failed to collect reliably all patient events – a fact that Plaintiffs do not dispute. *See* Pls.' Opp. at 62. With respect to non-fatal events, Madigan wrote a computer program to search the electronic data files for certain non-fatal terms or codes to count in his endpoints. *See* Defs.' Br. at 46-47. Plaintiffs suggest that Madigan relied on Baruch to validate this process, *see* Pls.' Br. at 62, but Baruch has no such recollection. *See* Defs.' Br. at 46-47. Plaintiffs also fail to address that Baruch could not provide critical details about the origin of the terms he reviewed with Madigan and other aspects of Madigan's undocumented process.[50] Neither Madigan nor Plaintiffs' counsel produced documentation of Madigan's non-fatal event counts or collection process, making it impossible to know which patients were counted, how they were counted, or whether the counts are correct.

Madigan's collection errors were not limited to non-fatal events. He also missed at least eight deaths, including four cardiovascular deaths in studies completed before December 16,

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[48] The spreadsheet that Madigan provided to Furberg to classify death events included events from trials comparing Celebrex to NSAIDs, but Madigan inexplicably ignored Furberg's classifications with regard to those trials and did not include them in his report. *See* Markel Decl., Ex. 13 at 212 (Madigan Dep. [testifying "counsel expressed more interest in confining it to the placebo . . . studies")]; Markel Opp. Decl., Ex. 198 (Madigan Ex. 20 Spreadsheet [including trials comparing Celebrex to NSAIDs]).

[49] *See* Markel Decl., Ex. 8 at 68 (Furberg Dep.); Markel Decl., Ex. 125 at 567 (Yusuf et al., EUR. HEART J. 1985;6:556-85 ["To be even moderately reliable, inference should be based on the totality of the available evidence, and not on outcome-dependent subsets of it . . . ."]); Markel Decl., Ex. 4 at 311 (FUNDAMENTALS OF CLINICAL TRIALS [" Many support the concept that the most valid overview or meta-analysis requires all studies conducted be available for inclusion or at least for consideration."]); Markel Decl., Ex. 5 at 25 (EVALUATING CLINICAL RESEARCH ["[E]xclusion of trials, for any reason, might itself introduce bias."]); *see also* Markel Opp. Decl., Ex. 179 at 260 (Boissel et al., CONTROLLED CLIN. TRIALS, 1989;10:254-81); Markel Decl., Ex. 3 at 306-07 (Bennett Dep., *In re Bextra*).

[50] For example, Baruch: (1) does not recall how he obtained the dictionary that he used, what version of the dictionary he used, or what level of terms were used, *see* Markel Decl., Ex. 161 at 57-58 (Baruch Dep.); (2) could not remember whether he discussed the terms with Madigan or advised him on the propriety of the three endpoints that Madigan chose, *see id.* at 41-43; and (3) did not recognize the documents that Plaintiffs represent as reflecting the search terms that Baruch endorsed, which led Baruch to admit he could offer no proof or validation that any of the terms Madigan used to search for "Hard CHD" or his other endpoints were valid ones to use. *See id.* at 163-65.

2004 – three in patients taking placebo and one in a patient taking Celebrex. *See* Markel Decl., Ex. 161 at 134-36 (Baruch Dep. [reviewing events in study reports that were not in the electronic data files]); *see also* App., Fig. 16. Setting aside the fact that these omissions bias his results against Celebrex, Madigan's failure to accurately collect events for inclusion in his meta-analysis alone would be sufficient to disqualify his meta-analysis for publication in a peer-reviewed journal. That failure also renders his opinions inadmissible here. Indeed, had Madigan properly included all death events, his myocardial thromboembolic endpoint would not have reached statistical significance.

3. Madigan's Methods for Counting Non-Fatal and Fatal Events Are Undocumented, Unprecedented, and Unreliable.

To enhance reliability, Plaintiffs' experts acknowledge that investigator-reported events should be verified through a process known as adjudication, *see* Defs.' Reply Br. at 35 n.54 *infra*, but there was no adjudication of the events included in Madigan's meta-analysis. Instead, Madigan counted non-fatal events one way and fatal events another. His methods with respect to both types of events are undocumented, unprecedented, and unreliable.

Madigan's Non-Fatal Event Collection Methodology Resulted in Numerous Errors. In analyzing non-fatal events, Madigan's computer program only searched the descriptions contained in the electronic data files, which contain only one-line, shorthand descriptions of patient events entered by data entry clerks. *See* Markel Decl., Ex. 13 at 52-53 (Madigan Dep.). When compared with the actual patient narratives – which were available to Madigan in the form of study reports and other sources that he chose to disregard – those shorthand descriptions and Madigan's apparent classifications turn out to be inaccurate in several instances. For example, Madigan's report lists one event as a non-cardiovascular event, even though the full patient narrative makes it clear that the event was in fact a cardiovascular death. *See* App., Fig. 17.

Madigan Cannot Authenticate the Fatal Event Counts Attributed to Baruch or Verify the Accuracy of the Counts. With regard to fatal events, Madigan gave Baruch a spreadsheet with a one-line snippet of each patient's death for Baruch to classify with no pre-specified

definitions for classifying the events.[51] At his deposition, however, Baruch testified that he has no recollection of that process, that the spreadsheet of event counts attributed to him is not the spreadsheet that he created,[52] and that he could not explain why he and Madigan relied on one-line descriptions when far more detailed patient information was available to them in the published literature, clinical trial reports and other records produced by Pfizer – information which would have more accurately captured what investigators and adjudication committees documented in the trials. *See* Markel Decl., Ex. 161 at 18-21, 154-55 (Baruch Dep.). Plaintiffs argue that Baruch's previous classification is irrelevant to this litigation because it occurred "more than one year ago in connection with a different case." Pls.' Opp. at 63-64. That argument overlooks that Baruch is a board certified cardiologist (and Plaintiffs' only cardiologist), and it implies that Madigan should be entitled to accept Baruch's work related to the classification of non-fatal events, but reject Baruch's prior diagnoses of fatal events simply because this is a new litigation – even though Madigan expressed no methodological concerns about Baruch's original analysis of either fatal or non-fatal events.

Madigan Cannot Authenticate the Recount of Fatal Events Attributed to Furberg or Validate Furberg's Unqualified, Unprecedented, and Unreliable Process. As noted in Pfizer's motion, Plaintiffs' counsel decided to have Furberg "redo" Baruch's count of fatal events only – but not his count of non-fatal events – even though Madigan could not offer a rationale for doing so. *See* Markel Decl., Ex. 13 at 44-45, 61 (Madigan Dep.). In addition to the fact that Furberg could not review all death events because Madigan did not extract them all from the electronic data files, Furberg's recount raises a number of methodological issues.

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[51] Markel Decl., Ex. 99 at 40 (Madigan Dep., *Grutka v. Pfizer*).

[52] Baruch's classification of these death events purportedly is reflected in a four-page spreadsheet identified as Exhibit 8 at Madigan's deposition. *See* Markel Opp. Decl., Ex. 197. Yet when Baruch was shown that document at his deposition, Baruch testified that it was not his spreadsheet and that the document contains an additional endpoint category – myocardial thromboembolic death, or "MTD" – that Baruch did not classify. *See* Markel Decl., Ex. 161 at 74 (Baruch Dep. ["It is not the one that I recall preparing . . . I don't have the MTD category."]). In their opposition, Plaintiffs do not dispute Baruch's testimony, and they have yet to produce the actual spreadsheet reflecting Baruch's classification of fatal events.

First, Furberg is not qualified to perform this unprecedented re-classification procedure. Plaintiffs spend much of their opposition extolling Furberg's qualifications to interpret clinical trial data generally. *See* Pls.' Opp. at 68-72. Yet Furberg's experience with interpreting clinical trial data does not render him qualified to adjudicate or to classify thrombotic cardiovascular events – a task Plaintiffs' experts agree must be performed by a board-certified cardiologist.[53] Plaintiffs also ignore that Furberg has not performed an adjudication in a clinical trial since the 1970s, when the diagnostic criteria for many conditions was much different than today. *See* Markel Decl., Ex. 8 at 361 (Furberg Dep.).

Even if qualified, Furberg himself admitted that his so-called "classification" – a term that does not exist in the literature – was something that he never had done before, either in litigation or outside of the courtroom. *See id.* at 365-66, 385-86. Furberg further testified that it was a challenge to classify events based solely on these single-line snippets and that he wished he had been given more information. *See id.* at 402-03, 409, 434-35; *see also id.* at 346 (describing the information as "not even a full line"). Bennett agrees. *See* Markel Opp. Decl., Ex. 183 at 70-71 (testifying that detailed patient information is necessary to perform valid adjudications). Plaintiffs' opposition gives the impression that a decision was made *not* to conduct an adjudication,[54] but Furberg testified that the only reason that he did not conduct a

[53] *See* Markel Opp. Decl., Ex. 183 at 69-70 (Bennett Dep. [testifying that "if you're looking at cardiovascular events, it's good to have a cardiologist review the data," and that "[o]ne would hope" the cardiologist is board certified]); *id.* at 72-73 (testifying that he is not qualified to adjudicate heart attacks because he is "not a cardiologist"). A doctor who does not specialize in treating patients in the relevant field is not qualified to determine or classify the causes of events. *See Gayton v. McCoy*, 521 F. Supp. 2d 841, 847-48 (C.D. Ill. 2007) (finding that a doctor who is not a cardiologist was not qualified to opine on cardiac-related cause of death); *Abdoush v. Jackson*, No. 2:06-CV-13554, 2007 WL 4557711 at *3-4 (E.D. Mich. Dec. 19, 2007) (affirming exclusion of doctor opining on cause of death in trauma surgery when his specialty was general surgery); *Prohaska v. Sofamor, S.N.C.*, 138 F. Supp. 2d 422, 436 (W.D.N.Y. 2001) (finding doctor not qualified to testify regarding differential diagnosis because he had not performed neurological surgery in the last four years, had not treated a patient with scoliosis – a condition relevant to the case – in the past ten years, and his area of specialty was not in the same as that at issue in the case).

[54] Plaintiffs also try to convince the Court that adjudication is a "manipulation" or "reengineering" of the data, *see* Pls.' Opp. at 9, but Plaintiffs' own experts agree that adjudication actually enhances the reliability of a meta-analysis. *See* Markel Decl., Ex. 8 at 134 (Furberg Dep.); Markel Decl., Ex. 13 at 63-65 (Madigan Dep.).

proper adjudication based on actual patient records was because "there was no time" in light of the deadline for his report. Markel Decl., Ex. 8 at 344 (Furberg Dep.).

Second, Furberg decided not to apply Madigan's pre-specified endpoints, but instead counted deaths according to his own definitions, which he neither recorded nor communicated to Madigan. *See id.* at 398-400, 403-04. He did so even thought he admits it is crucial for all researchers participating in a meta-analysis to apply the same definitions across all events. *See id.* at 434-35; *see also* Markel Decl., Ex. 7 at 769-70 (Furberg Dep., *Haslam v. Pfizer*). As a result of Furberg's unilateral, undocumented, and undisclosed decision to change the pre-specified definitions of fatal events, different definitions were applied to Madigan's counts of non-fatal events versus fatal events. *See* Markel Decl., Ex. 8 at 399, 403-04 (Furberg Dep.).

Third, Furberg's reclassification of Baruch's fatal event counts resulted in material differences between his counts and those of Baruch, but Madigan made no effort to reconcile the differences. Furberg testified that any discrepancies should have been reviewed, with any final decision resolved through a pre-defined process. *See* Markel Decl., Ex. 8 at 417-18 (Furberg Dep.). Furberg also agreed that it would be methodologically improper for Madigan simply to pick the counts he liked best. *See id.* at 417. Yet Madigan testified that he did just that, relying on Furberg's recounts without comparing them to Baruch's previous counts or reconciling any discrepancies. *See* Markel Decl., Ex. 13 at 67 (Madigan Dep.). Furberg's recounts also diverged from event counts determined by a formal adjudication committee in the NCI-sponsored APC and PreSAP trials, which Bennett and the entire medical community found to be reliable.[55]

Fourth, Plaintiffs do not dispute the fact that Furberg cannot authenticate the spreadsheet that Madigan claims contained Furberg's fatal event counts. *See* Markel Decl., Ex. 8 at 393-95,

[55] *Compare* Markel Decl., Ex. 97 at 30 (Madigan Rep. [listing 14 cardiovascular deaths for APC]) *with* Markel Decl., Ex. 134 at 1030-31 (Solomon, et al., CIRCULATION 2006;114:1028-1035 [listing 12 cardiovascular deaths for APC]); *see also* Markel Opp. Decl., Ex. 183 at 78 (Bennett Dep. [stating he is not aware of any circumstances in which it would be appropriate to change event counts from those conducted by the cardiovascular safety committees in the APC and PreSAP trials]); *id.* at 77 ("I think the event counts are trustworthy, certainly. . . I think that these were people who had expertise in these particular events, and I have no reason to doubt their ability.").

389 (Furberg Dep.). In fact, Furberg actually disagreed with the fatal event counts attributed to him in the spreadsheet that Madigan claims came from Furberg. The spreadsheet lists four deaths in the Alzheimer's 001 trial as fitting Madigan's "Hard CHD" endpoint. *See* Markel Opp. Decl., Ex. 198 (Madigan Ex. 20 Spreadsheet). At his deposition, however, after reviewing the same one-line snippets he was given by Plaintiffs' counsel, Furberg only could confirm that *one* Alzheimer's 001 death qualified as a "Hard CHD" event. *See* Markel Decl., Ex. 8 at 407-09 (Furberg Dep.); *see also* App., Fig. 18. It is only as a result of counting these four deaths in the Alzheimer's 001 trial against Celebrex – notwithstanding Furberg's testimony to the contrary – that Madigan's analysis of "Hard CHD events" reached statistical significance before December 2004, whereas Baruch's original classification did not. *See* Markel Decl., Ex. 13 at 175-76 (Madigan Dep.). This fact alone – putting aside whether such methods ever would survive a peer-review process outside of litigation – undermines Madigan's entire meta-analysis and renders his opinions inadmissible under *Daubert.*[56]

Furberg's reclassification of fatal events based only on the one-line snippets – rather than the available source information from which the snippets were drawn – neither honored the original conclusions of the investigators nor constitutes a reliable adjudication. The process Plaintiffs' experts followed is akin to counting the votes in an election, finding nothing wrong with the counting procedure, but doing a new recount with new rules in certain precincts only for no reason other than it provides a more favorable result. The Court should reject this unreliable exercise and find it to be inadmissible under *Daubert.*

III. NO STUDY OF BEXTRA PILLS SHOWED A STATISTICALLY SIGNIFICANT INCREASE IN THE RISK OF HEART ATTACKS AND STROKES

The totality of evidence today – from clinical trials, observational studies, and meta-analyses of clinical trials and observational studies – establishes that patients taking Bextra are at

[56] *See Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 596 (9th Cir. 1996) (affirming district court's exclusion of proposed expert testimony where the purported expert " 'has seen fit to 'pick and chose' [sic] from the scientific landscape and present the Court with what he believes the final picture looks like").

no greater risk of heart attacks and strokes than those taking other NSAIDs like Motrin or Aleve or no medication at all. Not even the parecoxib CABG trials – experimental studies involving high doses of intravenous parecoxib followed by high doses of oral Bextra pills in patients immediately after undergoing open heart surgery – showed a statistically significant association between the use of Bextra pills and thrombotic events such as heart attacks and strokes; rather, those trials only showed an increased risk when parecoxib, an unapproved drug, was used. Faced with that totality of evidence, Plaintiffs must resort to extrapolation from the parecoxib CABG trials, even though they fail to consider the different effects of parecoxib and Bextra pills and are not qualified to evaluate the unique physiology of patients undergoing CABG surgery.

A. The Totality of the Evidence Shows That Approved Doses of Bextra Are Safe in Real-World Patients and Are Comparable to Motrin and Aleve.

As with Celebrex, Plaintiffs spend their opposition trying to identify numerical imbalances which are not statistically significant in certain events in certain Bextra clinical trials. *See* Pls.' Opp. at 29-30, 35-37. Here, too, Plaintiffs do not focus on heart attacks and strokes (the events that are relevant to Pfizer's motion), but instead on events that are not used to evaluate heart attack and stroke risk, such as non-cardiovascular deaths in an experimental trial testing eight times the approved arthritis dose of Bextra to see whether that dose could help relieve the pain of terminally ill cancer patients and blood pressure results in another study evaluating four times and eight times the approved arthritis dose of Bextra.[57] Plaintiffs do not dispute that no clinical trial of Bextra pills alone (in the absence of parecoxib, a medication never approved for use in the United States) *ever* has shown a statistically significant increase in the risk of heart attacks, strokes, or heart attacks and strokes combined, whether Bextra was compared to placebo

[57] There is no evidence that any death in the 040 study was due to heart attack, stroke, or thrombotic causes. *See* Markel Reply Decl., Ex. 208 at 7, 14, 76 (040 Study Report). Further, data from the 047 study, which FDA evaluated prior to Bextra's approval, was described in the Bextra label from the first day it was on the market. *See* Markel Reply, Ex. 209 at 4 (Bextra Label, Apr. 2002). Moreover, patients in that study received very high doses of Bextra every day for six months, yet there were *no* heart attacks while patients were taking Bextra. *See id.*; Markel Reply Decl., Ex. 210 at 444-57 (047 Study Report, Table 46).

or other NSAIDs. *See* Defs.' Br. at 30-31. The lack of statistical significance in any thrombotic endpoint in any trial is striking. *See* Defs.' Br., App., Fig. 6.

Plaintiffs also do not deny that no published meta-analysis of the Bextra arthritis trials ever has shown a statistically significant increase in the risk of heart attacks, strokes, or heart attacks and strokes combined, whether Bextra was compared to placebo or other NSAIDs.[58] Nor do Plaintiffs refute that observational studies, including one authored by David Graham of the FDA (whom Plaintiffs cite in their brief, *see* Pls.' Opp. at 3), reached the same finding – that real-world patients taking approved doses of Bextra for the treatment of arthritis are at no greater risk of thrombotic events than patients taking other NSAIDs or no NSAIDs at all.[59]

Similarly, Plaintiffs ignore the FDA's conclusions that there was no evidence that real-world patients taking Bextra pills for approved uses were at any greater risk of heart attacks and strokes and that Bextra was no less safe for the heart than Motrin or Aleve. *See* Defs.' Br. at 35 (quoting David Graham ["[T]he information we have at this time suggests that the risk is not increased at doses of 20 mg or less."]); *id.* at 36 (quoting FDA Decision Mem.). Plaintiffs also do not dispute that Bextra was withdrawn from the market because of an increased risk of very rare skin reactions compared to other NSAIDs, not because of a unique cardiovascular concern that distinguished Bextra from other NSAIDs. *See id.* at 36 (citing FDA Decision Mem.).

B. The Parecoxib CABG Surgery Trials Do Not Establish Thrombotic Risk for Oral Bextra Pills.

Faced with this totality of evidence, Plaintiffs rely almost exclusively on the experimental, high-dose intravenous parecoxib CABG surgery trials to establish an increased

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[58] *See* Defs.' Br. at 36-37 & n.43 (citing Chen, Edwards, Kearney, and White); *see* Markel Decl., Ex. 3 at 522-24 (Bennett Dep., *In re Bextra* [conceding that Chen shows no increased risk]); Markel Opp. Decl., Ex. 183 at 199-200 (Bennett Dep. [admitting that Chen shows "no difference" between Bextra and naproxen (Aleve)]). Plaintiffs cite a non-statistically significant meta-analysis Pfizer submitted to EMEA, but even that excerpt notes that EMEA found only that Bextra has the "potential" to cause cardiovascular toxicity. *See* Pls.' Opp. at 36.

[59] *See* Defs.' Br. at 36 (citing Solomon); *see also* Markel Reply Decl., Ex. 211 at 10 (Singh et al., *Concomitant Aspirin Use Reduces Acute Myocardial Infarction Risk in Cyclooxygenase-2 Selective Nonsteroidal Anti-Inflammatory Drug Users*, unpublished [David Graham, co-author]).

heart attack and stroke risk associated with the use of oral Bextra. Yet even those trials do not demonstrate a statistically significant increase in the risk of heart attacks and strokes for patients taking oral Bextra pills alone, as Plaintiffs' experts admit. Moreover, Plaintiffs' experts failed to consider the different cardiovascular effects of intravenous parecoxib, a medication never approved for use in the United States, and approved Bextra pills, and they are not qualified to evaluate the unique physiology of CABG surgery patients. Accordingly, the Court should reject Plaintiffs' experts' unreliable methodology and find their CABG surgery opinions inadmissible.

1. Plaintiffs' Experts' Methods That Rely on Intravenous Parecoxib Data Are Unreliable Because the CABG Surgery Trials Do Not Demonstrate a Statistically Significant Increase in Thrombotic Risk for Patients Taking Oral Bextra Pills.

Plaintiffs argue that there is a statistically significant incidence of serious adverse events in the CABG-1 trial. *See* Pls.' Opp. at 31. The overall incidence of any adverse event, including events other than heart attack or stroke, does not establish that Bextra increases thrombotic risk, so that data is irrelevant to Pfizer's motion. Plaintiffs do not dispute that the imbalance was driven mainly by a single adverse event – infections of the sternal wound created when a bypass patient's chest is cut open – which has no relevance to an arthritis patient, let alone heart attacks and strokes. *See* Markel Decl., Ex. 82 at 1481 (Ott). For the thrombotic events relevant to this case, Plaintiffs' expert Kronmal admits that the results from CABG-1, even when combining the parecoxib and oral Bextra pill data, were not statistically significant. *See* Pls.' Opp. at 31; Markel Decl., Ex. 2 at 9 (Kronmal Rep. [conceding non-significant results for thrombotic events in parecoxib CABG-1 trial]). Similarly, in his editorial, Furberg admits that CABG-1 showed no statistically significant increased risk of coronary and cerebrovascular events – thereby relying on statistical significance and a *p*-value threshold of 0.05, contrary to the arguments of Plaintiffs' counsel. *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249).

In their argument regarding CABG-2, Plaintiffs again cite the incidence of all adverse events, *see* Pls.' Opp. at 32, but that again does not establish an increased thrombotic risk for heart attacks and strokes. In addition, Plaintiffs claim there was a statistically significant

increased risk of major cardiovascular events with Bextra, but that is only true for the patients who received experimental, high-dose intravenous parecoxib followed by high-dose oral Bextra pills ("the parecoxib / oral Bextra pills group"); the group receiving oral Bextra pills only did not show an increased risk, nor were the results statistically significant when the study authors *combined* the data from the parecoxib / oral Bextra pills group with the data from the oral Bextra pills only group. *See* Markel Decl., Ex. 87 at 1087, Table 3 (Nussmeier). Kronmal admits that the CABG-2 study did not show a statistically significant increase in risk for the group taking oral Bextra pills only. *See* Markel Decl., Ex. 12 at 334-35 (Kronmal Dep.). Likewise, Furberg's editorial concedes that the thrombotic events in CABG-2 did not show a statistically significant increase in risk. *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249).

2. Plaintiffs' Experts' Opinions Ignore the Differences Between Experimental, Intravenous Parecoxib and Oral Bextra Pills.

Even though the parecoxib CABG study data do not show a statistically significant increase in the risk of heart attacks and strokes for patients taking oral Bextra pills, Plaintiffs still attempt to extrapolate from those studies to patients taking approved doses for arthritis, claiming that oral Bextra pills and intravenous parecoxib, a medication never approved for use in the U.S., exert the same effects. *See* Pls.' Opp. at 33-34. Yet Plaintiffs' experts ignore evidence that undercuts their opinion, and do not even attempt to explain the differences in effects seen with intravenous parecoxib compared to oral Bextra pills, even though they have conceded outside of litigation that intravenous formulations can have different effects than oral pills.[60]

Here, Plaintiffs' experts admit that they ignored the different cardiovascular effects seen with use of the unapproved, intravenous parecoxib. For example, Furberg believes unequivocally that Bextra increases blood pressure, but he offers no explanation for the fact that parecoxib significantly *decreased* blood pressure in both CABG trials, as the FDA noted.[61]

[60] *See* Markel Decl., Ex. 7 at 362-65 (Furberg Dep., *Haslam v. Pfizer*); *see also* Defs.' Br. at 65 n.68.

[61] *See* Markel Decl., Ex. 7 at 207-08 (Furberg Dep., *Haslam v. Pfizer*); Markel Decl. Ex. 23 at 507 (FDA Ad. Comm. Tr., Feb. 16, 2005); Markel Decl., Ex. 81 at 2 (FDA Parecoxib Sodium Non-Approvable Ltr.).

Baruch admitted having done no research on or analysis of the different clinical effects of parecoxib and oral Bextra pills – such as the concentrations they reach in the human body – and their different cardiovascular effects.[62] Plaintiffs' other experts similarly failed to consider differences between the effects of parecoxib and oral Bextra pills.[63] Where an expert fails to consider whether his assumptions are correct, that expert should be excluded under *Daubert*.[64]

3. Plaintiffs' Experts Lack the Expertise to Evaluate the Unique Physiology of CABG Surgery Patients.

In addition to failing to consider the different cardiovascular effects of intravenous parecoxib and oral Bextra pills, Plaintiffs' experts also fail to account for the physiological differences between CABG surgery patients and arthritis patients. *See* Markel Decl., Ex. 3 at 246-47 (Furberg Dep.); Markel Decl., Ex. 7 at 189-92 (Furberg Dep., *Haslam v. Pfizer*). They fail to do so even though they have admitted that researchers only can apply clinical trial results reliably to the population from which the trial was drawn. *See* Defs.' Br. at 66 (citing Furberg articles). In fact, Furberg has admitted that surgical populations differ from outpatients. *See* Markel Decl., Ex. 23 at 527-28 (Ad. Comm. Tr.). Those that claim to have considered the physiological differences – including the statistician Kronmal[65] and Baruch[66] – are unqualified to

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[62] *See* Markel Decl., Ex. 161 at 189-92 (Baruch Dep.). Baruch admits that the method of administration can affect the blood levels of a medication, but he does not know how the blood levels differ with intravenous parecoxib compared to oral Bextra pills. *See id.* at 190-92. When asked whether different blood levels could result in different thrombotic effects, Baruch admitted that he did not know. *See id.* at 196-97.

[63] *See* Markel Decl., Ex. 12 at 6, 317-18 (Kronmal Dep. [admitting he did not evaluate how the effects of intravenous parecoxib differ from those of oral Bextra pills]); Markel Opp. Decl., Ex. 183 at 123-24 (Bennett Dep. [admitting that intravenous parecoxib could exert different effects than oral Bextra pills]); *id.* at 219 (conceding that unsafe *drops* in blood pressure, known as hypotension, could be a potential explanation for the increase in thrombotic events seen in the CABG trials).

[64] *See In re Baycol Prod. Litig.*, 532 F. Supp. 2d 1029, 1046 (D. Minn. 2007) (excluding expert's testimony based on unsupported assumptions); *Hamilton v. Emerson Elec. Co.*, 133 F. Supp. 2d 360, 371-72 (M.D. Penn. 2001) (same).

[65] Plaintiffs concede that Kronmal is not qualified to make medical judgments about whether it is appropriate to compare the physiology of patients undergoing CABG surgery to that of patients in the general arthritis population, claiming that he was charged only with assessing Bextra from a "statistical perspective." Pls.' Opp. at 90; *see* Markel Decl., Ex. 12 at 6, 124-27 (Kronmal Dep. [admitting he does not have a medical degree, is not a cardiologist, and never would treat a patient]); *see also* Markel Decl. Ex. 132 at 234-35 (Jewell Dep., *In re Bextra/Haslam v. Pfizer* [acknowledging a researcher requires more than just statistical expertise to generalize results]).

assess the impact of CABG surgery on the risk of thrombotic events after surgery or admit that the mechanism of heart attacks in post-CABG patients is "not exactly the same" as in the general population. Markel Decl., Ex. 161 at 205-06 (Baruch Dep.).

Indeed, because of the differences between CABG surgery patients taking experimental, high-dose, intravenous parecoxib and arthritis patients taking arthritis doses of oral Bextra pills, two different journals rejected Furberg's attempt to group the CABG surgery trials with the arthritis trials – a fact Plaintiffs ignore altogether.[67] Even Furberg questioned in his editorial – co-written with Dr. Garret FitzGerald – whether the results from the CABG surgery setting were applicable to an arthritis population taking lower, approved doses. *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249 ["It is currently unclear to what degree such risk extends to patients treated chronically with lower doses for arthritis. . . ."]).

Bennett, the only Plaintiffs' expert who evaluated how Bextra and Celebrex supposedly work in the body, and who has studied the function of platelets in the context of CABG surgery, believes that the CABG surgery environment differs significantly from a patient's ordinary physiology. "[T]his is a completely different setting. So I'm not sure you could legitimately or logically extrapolate from going on a bypass machine to treating swollen joints." Markel Opp. Decl. Ex. 183 at 137 (Bennett Dep.); *see also id.* at 120-23; Markel Decl. Ex. 3 at 466-68 (Bennett Dep., *In re Bextra*). As a result, Bennett concedes that it is improper to "extrapolate findings from [bypass surgery] data to people taking the drug in the real world for arthritis" – thereby rejecting the very basis of Plaintiffs' other experts' opinions regarding those trials. Markel Decl. Ex. 3 at 328-29 (Bennett Dep., *In re Bextra*); *see* Markel Opp. Decl., Ex. 183 at

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[66] Plaintiffs argue that Baruch is qualified simply because he is a cardiologist and occasionally sees patients who have undergone CABG surgery. *See* Pls.' Opp. at 93-94. Yet Plaintiffs fail to address the fact that Baruch himself admitted that he is not qualified to discuss how CABG surgery affects clotting – the very mechanism by which Plaintiffs claim Bextra causes heart attacks and strokes. *See* Markel Decl., Ex. 161 at 202-06 (Baruch Dep.).

[67] *See* Markel Decl., Ex. 7 at 313-15, 320, 351-52 (Furberg Dep., *Haslam v. Pfizer*); Markel Opp. Decl., Ex. 199 at 1 (CIRCULATION, Valdecoxib and Cardiovascular Risk: An Updated Meta-analysis: Transaction History). Similarly, other meta-analyses on which Furberg has relied do not lump together the oral Bextra pill arm with the patients taking both high-dose, intravenous parecoxib and oral Bextra pills. *See* Markel Reply Decl., Ex. 212 at 3, 6 (Aldington et al., N. ZEALAND MED. J. 2005;118:U1755); Markel Decl., Ex. 1, App. B. (Furberg Rep.).

124 (Bennett Dep. ["Well, it's a different clinical situation, so I wouldn't extrapolate."]). Plaintiffs also overlook comments by the FDA and other experts in the field who questioned the applicability of the CABG surgery trials to real-world arthritis patients.[68]

Plaintiffs also argue that their experts' reliance on the CABG studies raises a "fact question," which does not bear on the admissibility of Plaintiffs' experts' opinions. *See* Pls.' Opp. at 33. That is incorrect. Whether an opinion is supported by a reliable methodology and foundation is precisely the question *Daubert* is meant to address, and expert opinions must be excluded when the extrapolation methodology is unreliable or unfounded.[69] Because the "analytical gap" between the data from the CABG surgery trials and Plaintiffs' experts' opinions is so great, their CABG extrapolation opinions do not survive review under *Daubert*. *In re Bextra I*, 524 F. Supp. 2d at 1181 (citing *Joiner*, 522 U.S. at 146, and excluding expert testimony where the gap between the data and the expert's conclusion was "simply too great to make the opinion admissible").

CONCLUSION

For the foregoing reasons, the Court should grant Pfizer's motion to exclude the testimony of Plaintiffs' experts that prior to December 16, 2004, there existed reliable scientific evidence that Celebrex and/or Bextra were associated with a statistically significant increase in the risk of thrombotic cardiovascular events such as heart attacks and strokes.

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[68] *See* Defs.' Br. at 35-36 & n.42 (citing Markel Decl., Ex. 55 at 9 [FDA Decision Mem.]); *see also* Markel Decl. Ex. 23 at 489 (Ad. Comm. Tr., Feb. 16, 2005 [Dr. Seibert]); *id.*, Feb. 18, 2005 at 302 (Dr. Abramson: "[I]t is very hard for me to extrapolate results in that population to a general population."); Markel Decl., Ex. 57 at 12 (FDA Ad. Comm. Minutes ["In general, the Committee felt that the evidence was very limited and it is difficult to extrapolate [the CABG results] to a real life setting."]); Markel Reply Decl., Ex. 213 at 60-62, 80 (Goldkind Dep., *In re Bextra*).

[69] *See, e.g., In re Bextra*, 524 F. Supp. 2d at 1171, 1180-81 (listing "whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion" as a factor in assessing the reliability of expert testimony and excluding plaintiffs' expert opinions based on unreliable extrapolation); *see also McClain v. Metabolife Int'l, Inc.*, 401 F.3d. 1233, 1245 (11th Cir. 2005); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1208 (10th Cir. 2002).

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APPENDIX

Figure 13

Comparison of Prescription Drugs with Type A and Type B Safety Concerns

Prescription Drugs With a Type A Safety Concern Identified				
Name of Drug	**Year of FDA Action**	**Nature of the Safety Issue**	**Risk ratios, confidence intervals and P-values calculated**	**Statistical significance used as the basis for determining presence of a true drug effect**
Drugs Withdrawn From US Market Because of a Type A Safety Concern (1975-2007)				
Azaribine	1976	Myocardial infarction, venous thromboembolic events[1-3]	Yes	Yes
Phenacetin	1985	Renal failure[4-6]	Yes	Yes
Encainide	1991	Cardiovascular death[9]	Yes	Yes
Flosequinan	1993	Cardiovascular death[10]	Yes	Yes
Dexfenfluramine Fenfluramine/ phenteramine	1997	Valvular heart disease[11-15]	Yes	Yes
Mibefradil	1998	Death[16]	Yes	Yes
Alosetron	2000	Constipation, ischemic colitis[17-20]	Yes	Yes
Phenylpro-panolamine	2000	Hemorrhagic stroke[21-25]	Yes	Yes
Rapacuronium (Raplon)	2001	Bronchospasm following induction of anesthesia[26, 27]	Yes	Yes
Rofecoxib	2004	Myocardial infarction and stroke[28-37]	Yes	Yes
Tegaserod	2007	Myocardial infarction, stroke, unstable angina pectoris[38]	Yes	Yes
Pergolide	2007	Valvular heart disease[39-46]	Yes	Yes
Aprotinin	2007	Death[47-52]	Yes	Yes
US Drugs With New Boxed Warning or Withdrawn from Market Due to a Type A Safety Concern (July 2007 – June 2009)				
Pioglitazone Rosiglitazone	2007	Heart failure[53-59]	Yes	Yes
Rosiglitazone	2007	Myocardial ischemic events (*e.g.*, myocardial infarction) [60-69]	Yes	Yes
Becaplermin	2008	Death due to cancer[70]	Yes	Yes
Fluoroquinolone antibiotics	2008	Tendonitis and tendon rupture[71-73]	Yes	Yes
Various antipsychotics	2008	Death[74-82]	Yes	Yes
Atomoxetine	2008	Suicidal thoughts[83]	Yes	Yes
Trastuzumab	2008	Cardiac dysfunction and heart failure[84-89]	Yes	Yes
Estrogen and combined estrogen-progestins	2008	Dementia and cognitive decline[90, 91]	Yes	Yes
Epoetin alfa Darbepoetin	2007	Cardiovascular death, myocardial infarction, stroke and heart failure in patients with chronic kidney disease[92, 93]	Yes	Yes
	2008	Death in patients with cancer[94-99]	Yes	Yes

Prescription Drugs With a Type B Safety Concern Identified				
Name of Drug	**Year of FDA Action**	**Nature of the Safety Issue**	**Risk ratios, confidence intervals and P-values calculated**	**Statistical significance used as the basis for determining presence of a true drug effect**
Drugs Withdrawn From US Market Because of a Type B Safety Concern (1975-2005)				
Phenformin	1978	Spontaneous lactic acidosis in non-insulin-dependent diabetics[100-103]	No	No
Ticrynafen	1980	Autoimmune hepatitis due to anti-liver microsomal antibodies that target P450[104-108]	No	No
Benoxaprofen	1982	Fatal cholestatic jaundice associated with renal failure[109-112]	No	No
Zomepirac	1983	Anaphylaxis and hypersensitivity reactions[113-115]	No in case series; yes in observational studies	No in case series; yes in observational studies
Oxyphenbutazone	1985	Fatal immune-mediated aplastic anemia and agranulocytosis[116-118]	No	No
Pituitary growth hormone	1985	Creutzfeldt-Jacob disease[119]	No	No
Nomifensine	1986	Immune-mediated hemolytic anemia[120, 121]	No	No
Suprofen	1987	Flank pain syndrome due to acute diffuse crystallization of uric acid in renal tubules[122, 123]	No	No
Guar gum	1991	Acute esophageal and small bowel obstruction due to drug plugging[124, 125]	No	No
Clozapine	1992	Nonchemotherapy-related agranulocytosis[126-130]	No	No
Temafloxacin	1992	Acute immune-mediated hemolysis and renal dysfunction[131, 132]	No	No
Terfenadine	1997	Drug-induced torsade de pointes[133-136]	No	No
Bromfenac (Duract)	1998	Spontaneous fulminant liver failure leading to death or transplatation[137-140]	No	No
Astemizole	1999	Drug-induced torsade de pointes[141]	No	No
Grepafloxacin	1999	Drug-induced torsade de pointes[142]	No	No
Troglitazone	2000	Fulminant hepatic failure leading to death or transplantation[143-147]	No	No
Cisapride	2000	Drug-induced torsade de pointes[148-150]	No	No
Cerivastatin	2001	Rhabdomyolysis, often followed by renal failure[151-155]	No	No
Etretinate	2002	Teratogen-mediated embryopathy[156-158]	No	No
Levomethadyl	2003	Drug-induced torsade de pointes[159, 160]	No	No
Pemoline	2005	Fulminant hepatic failure in children and adolescents[161-163]	No	No
Valdecoxib	2005	Stevens-Johnson syndrome[164-166]	No	No
Natalizumab	2005	Progressive multifocal leukoencephalopathy[167-169]	No	No
99m Tc fanolesomab	2005	Sudden unexplained cardiopulmonary reactions[170]	No	No
Hydromorphone (Palladone)	2005	Potential for serious overexposure to drug due to dose dumping if drug is taken with alcohol[171, 172]	No	No

Prescription Drugs With a Type B Safety Concern Identified				
Name of Drug	**Year of FDA Action**	**Nature of the Safety Issue**	**Risk ratios, confidence intervals and P-values calculated**	**Statistical significance used as the basis for determining presence of a true drug effect**
US Drugs With New Boxed Warning or Withdrawn from Market Due to a Type B Safety Concern (July 2007 – June 2009)				
Mycophenolate	2007	Unusual congenital malformations[173-175]	No	No
Alglucosidase	2008	Severe infusion reactions, including anaphylaxis[176, 177]	No	No
Denileukin	2008	Capillary leak syndrome; can be severe and fatal[177-182]	No	No
Entecavir	2008	Emergence of variant associated with resistance to drugs used to treat HIV[183, 184]	No	No
Perflutren	2008	Serious cardiopulmonary reactions within 30 minutes of injection[185]	No	No
Laronidase	2008	Severe infusion reactions, including anaphylaxis[186]	No	No
Nevirapine	2008	Stevens-Johnson syndrome; fulminant hepatic failure[187-190]	No	No
Rituximab	2008	Serious infusion reactions[191-194]	No	No
Lapatinib	2008	Fulminant hepatic failure leading to death[195, 196]	No	No
Efalizumab	2009	Progressive multifocal leukoencephalopathy[197]	No	No
Sodium phosphate bowel preparations	2009	Sudden (often irreversible) renal failure due to acute phosphate nephropathy[198-203]	No	No
Infliximab	2009	EBV-negative hepato-splenic T-cell lymphoma[204-207]	No	No
Metoclopramide	2009	Tardive dyskinesia[208-213]	No	No

Notes

[1] Markel Reply Decl., Ex. 214 (Wardell WM et al., J. CLIN. PHARMACOL. 1979;19:169-84).
[2] Markel Reply Decl., Ex. 215 (Drell W et al., PHARMACOL. THER. 1989;41:195-206).
[3] Markel Reply Decl., Ex. 216 (Shupack JL et al., ARCH. DERMATOL. 1977;113:1301-2).
[4] Markel Reply Decl., Ex. 217 (Buckalew VM Jr et al., MEDICINE (BALTIMORE) 1986;65:291-303).
[5] Markel Reply Decl., Ex. 218 (Gonwa TA et al., ARCH. INTERN. MED. 1981;141:462-65).
[6] Markel Reply Decl., Ex. 219 (Cove-Smith JR et al., Q. J. MED. 1978;47:49-69).
[7] Markel Reply Decl., Ex. 220 (Morlans M et al., BR. J. CLIN. PHARMACOL. 1990;30:717-23).
[8] Markel Reply Decl., Ex. 221 (Pommer W et al., AM. J. NEPHROL. 1989;9:403-12).
[9] Markel Reply Decl., Ex. 222 (Echt DS et al., N. ENGL. J. MED. 199;324:781-88).
[10] Markel Reply Decl., Ex. 223 (Moe GW et al., AM. HEART. J. 2000;139:587-95).
[11] Markel Reply Decl., Ex. 224 (Centers for Disease Control and Prevention, MORB. MORTAL. WKLY. REP. 1997;46:1061-6).
[12] Markel Reply Decl., Ex. 225 (Khan MA, et al., N. ENGL. J. MED. 1998;339:713-18).
[13] Markel Reply Decl., Ex. 226 (Jick H et al., N. ENGL. J. MED. 1998;339:719-24).
[14] Markel Reply Decl., Ex. 227 (Ryan DH et al., OBES. RES. 1999;7:313-22).
[15] Markel Reply Decl., Ex. 228 (Gardin JM et al., JAMA 2000;283:1703-9).
[16] Markel Reply Decl., Ex. 229 (Levine TB et al., CIRCULATION 2000;101:758-64).
[17] Markel Reply Decl., Ex. 230 (Rahimi R et al., CLIN. THER. 2008;30:884-901).
[18] Markel Reply Decl., Ex. 231 (Andresen V et al., CLIN. GASTROENTEROL. HEPATOL. 2008;6:545-55).
[19] Markel Reply Decl., Ex. 232 (Gallo-Torres H et al., AM. J. GASTROENTEROL. 2006;101:1080-3).
[20] Markel Reply Decl., Ex. 233 (Chang L et al., AM. J. GASTROENTEROL. 2006;101:1069-79).

[21] Markel Reply Decl., Ex. 234 (Lake CR et al., AM. J. MED. 1990;89:195-208).
[22] Markel Reply Decl., Ex. 235 (Kernan WN et al., N. ENGL. J. MED. 2000;343:1826-32).
[23] Markel Reply Decl., Ex. 236 (Cantu C et al., STROKE 2003;34:1667-72).
[24] Markel Reply Decl., Ex. 237 (Mersfelder TL, CLEVE. CLIN. J. MED. 2001;68:208-9, 213-9, 223).
[25] Markel Reply Decl., Ex. 238 (Yoon BW et al., NEUROLOGY 2007;68:146-9).
[26] Markel Reply Decl., Ex. 239 (Meakin GH et al., ANESTHESIOLOGY 2001;94:926-7).
[27] Markel Reply Decl., Ex. 240 (Rajchert DM et al., ANESTH. ANALG. 2002;94:488-93).
[28] Markel Decl., Ex. 27 (Bombardier C et al., N. ENGL. J. MED. 2000;343:1520-8).
[29] Markel Decl., Ex. 29 (Bresalier RS et al., N. ENGL. J. MED. 2005;352:1092-102).
[30] Markel Reply Decl., Ex. 241 (Kerr DJ et al., N. ENGL. J. MED. 2007;357:360-9).
[31] Markel Reply Decl., Ex. 242 (Jüni P et al., LANCET 2004;364:2021-9).
[32] Markel Decl., Ex. 38 (Solomon DH et al., CIRCULATION 2004;109:2068-73).
[33] Markel Decl., Ex. 34 (Hippisley-Cox J et al., BMJ. 2005;330:1366).
[34] Markel Decl., Ex. 33 (Graham DJ et al., LANCET 2005;365:475-81).
[35] Markel Reply Decl., Ex. 243 (Velentgas P et al., PHARMACOEPIDEMIOL. DRUG SAF. 2006;15:641-52).
[36] Markel Decl., Ex. 91 (Solomon DH et al., ARTHRITIS RHEUM. 2006;54:1378-89).
[37] Markel Decl., Ex. 37 (McGettigan).
[38] Markel Reply Decl., Ex. 244 (Press Release, Novartis, Novartis suspends Canadian marketing and sales of ZelnormI in response to request from Health Canada (March 30, 2007)).
[39] Markel Reply Decl., Ex. 245 (FDA Public Health Advisory, Pergolide (marketed as Permax) (March 29, 2007)).
[40] Markel Reply Decl., Ex. 246 (Steiger M et al., J. NEURAL. TRANSM. 2009;116:179-91).
[41] Markel Reply Decl., Ex. 247 (Zadikoff C et al., CAN. J. NEUROL. SCI. 2008;35:173-8).
[42] Markel Reply Decl., Ex. 248 (Yamashiro K et al., MOV. DISORD. 2008;23:935-41).
[43] Markel Reply Decl., Ex. 249 (Corvol JC et al., ARCH. NEUROL. 2007;64:1721-6).
[44] Markel Reply Decl., Ex. 250 (Dewey RB 2nd et al., ARCH. NEUROL. 2007;64:377-80).
[45] Markel Reply Decl., Ex. 251 (Zanettini R et al., N. ENGL. J. MED. 2007;356:39-46).
[46] Markel Reply Decl., Ex. 252 (Van Camp G et al., LANCET 2004;363:1179-83).
[47] Markel Reply Decl., Ex. 253 (Takagi H, et al., INTERACT. CARDIOVASC. THORAC. SURG. 2009l;9:98-101).
[48] Markel Reply Decl., Ex. 254 (Gagne JJ et al., PHARMACOEPIDEMIOL. DRUG SAF. 2009;18:259-68).
[49] Markel Reply Decl., Ex. 255 (Fergusson DA et al., N. ENGL. J. MED. 2008;358:2319-31).
[50] Markel Reply Decl., Ex. 256 (Shaw AD et al., N. ENGL. J. MED. 2008;358:784-93).
[51] Markel Reply Decl., Ex. 257 (Schneeweiss S et al., N. ENGL. J. MED. 2008;358:771-83).
[52] Markel Reply Decl., Ex. 258 (Mangano DT et al., JAMA 2007;297:471-9).
[53] Markel Decl., Ex. 160 (Lincoff AM et al., JAMA 2007;298:1180-8).
[54] Markel Reply Decl., Ex. 259 (Singh S et al., DIABETES CARE 2007;30:2148-53).
[55] Markel Reply Decl., Ex. 260 (DREAM Trial Investigators, et al., DIABETES CARE 2008;31:1007-14).
[56] Markel Reply Decl., Ex. 261 (Lago RM et al., LANCET 2007;370:1129-36).
[57] Markel Reply Decl., Ex. 262 (Dargie HJ et al., J. AM. COLL. CARDIOL. 2007;49:1696-704).
[58] Markel Reply Decl., Ex. 263 (DREAM Trial Investigators et al., LANCET 2006;368:1096-105.)
[59] Markel Reply Decl., Ex. 264 (Hartung DM et al., PHARMACOTHERAPY 2005;25:1329-36).
[60] Markel Reply Decl., Ex. 265 (Lipscombe LL et al., JAMA 2007;298:2634-43).
[61] Markel Decl., Ex. 156 (Singh S et al., JAMA 2007;298:1189-95).
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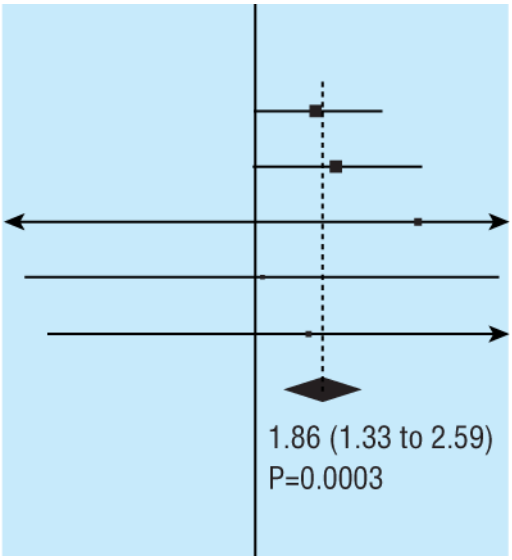
Figure 14

Myocardial infarction			
Rofecoxib	37	54/6638	30/6415
Celecoxib	41	44/8976	9/4953
Etoricoxib	17	2/753	0/414
Lumiracoxib	12	5/1375	2/584
Valdecoxib	14	8/748	1/273
Subtotal	121	113/18 490 (0.6%/year)	42/12 639 (0.3%/year)

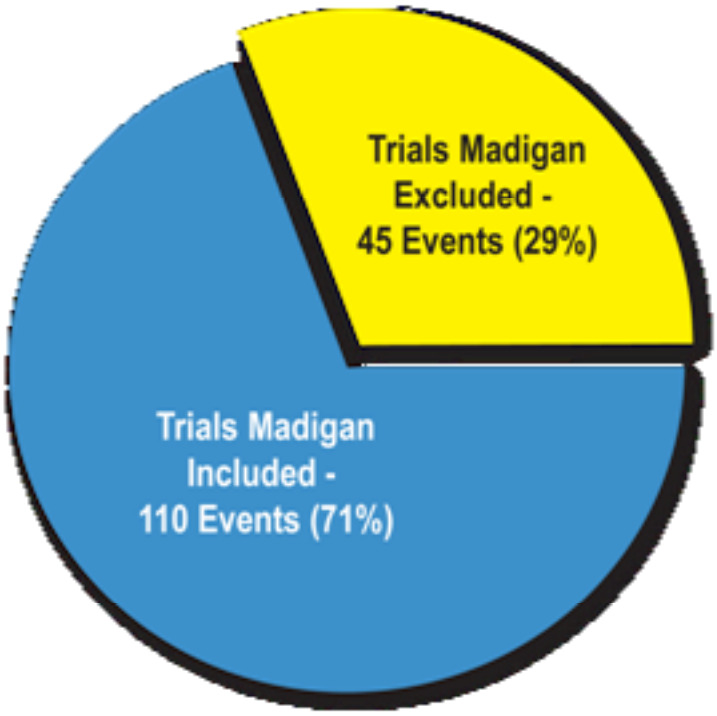
Heterogeneity between five drugs: χ^2=1.0, df=4, P=0.9



Notes:
[1] Markel Opp. Decl., Ex. 174 at 1304 (Kearney [Figure 1]).

Figure 15

Madigan's Meta-Analysis Considered Only 71% of the Thrombotic Events in the Celebrex Placebo-Controlled Trials.[1]



Placebo-Controlled Trials Madigan Excluded	
Trial	**Statistically Significant Increase of CV Risk?**
COXA-0508-253	NO
N49-01-02-198	NO
N49-01-02-201	NO
COXA-0508-146	NO
NQ5-98-02-005	NO
NQ8-00-02-004	NO
20010836	NO
COXXNT-6570-001	NO
N49-01-02-200	NO
221_ALS	NO
ADAPT	NO

Notes:
[1] *See* Defs.' Opp. to Pls.' Mot. to Exclude Pfizer Expert, Lee-Jen Wei, Ph.D. at App., Fig. 12.

Figure 16

Madigan Missed At Least Eight Deaths, Including the Following Four Cardiovascular Deaths from Trials before December 16, 2004.

Trial	Patient ID	Drug/Placebo	Plaintiffs' Response[1]
COXXNT-6570-0001	90070	Placebo	Do not address
EQ5-98-02-002	916	Placebo	Concede event was missed
635-IFL-0508-003	1025-1382	Placebo	Concede event was missed
N49-98-02-087	0021-0182	Celebrex	Concede event was missed

Notes:
[1] *See* Pls.' Opp. at 62. Plaintiffs' opposition concedes that three of the above four deaths were missed but fail to explain why, if they could identify them in their opposition, Madigan could not employ the same methods when he conducted his initial analysis. Plaintiffs also mistakenly identify a death from Celebrex patient 0033-0768 from the N49-96-02020 trial as one of the missing deaths, continuing to overlook the death of placebo patient 90070 from the COXXNT-6570-001 trial. *See* Markel Reply Decl., Ex. 416 at Clinical Trials 00502251 (COXXNT-6570-001 Study Report).

Figure 17

One-Line Snippets vs. Patient Narratives

Trial & Patient ID	One-Line Description Provided by Madigan	Patient Narrative From Study Report	Furberg's Classification Based On One-Line Description	Adjudication by Three Board-Certified Cardiologists Based On Patient Narratives
CLASS Patient # 102-20518	"Cardiopulmonary arrest"[1]	"**Patient US0270-102-20518** (cardiac arrest): [Patient] is a 75 year old female with a history of pericardial effusion — rheumatoid pericarditis 1991 without recurrence, emphysema, chronic obstructive pulmonary disease – mild in 1992, diverticulitis, colon resection – 1991 with a colostomy which was closed on 1993, no history of coronary artery disease, and rheumatoid arthritis. … On February 9, 1999, the patient called 911 complaining of shortness of breath and was found unresponsive and in cardiac arrest by emergency medical services. … Per the investigator, the patient with a history of chronic obstructive pulmonary disease, had been having symptoms of a upper respiratory infection, complained of shortness of breath and **was found dead presumably from bronchitis.** … The investigator feels that this event is not associated with the study medication. … Per the county coroner pathologist review of the patient's charts, he concluded that the **cause of death was the patient's chronic obstructive pulmonary disease.**"[2]	Cardiovascular death[1]	Noncardiovascular event[3]

Notes:
[1] Markel Decl., Ex. 198 (Madigan Ex. 20 Spreadsheet).
[2] Markel Reply Decl., Ex. 417 at Clinical Trials 00455928 (CLASS Study Report) (emphasis added).
[3] *See* Markel Reply Decl., Ex. 418 at 3-5 (Cardiologists Adjudication Combined, PFE ADJUD 00600-604).

Figure 17 (con't)

Trial & Patient ID	One-Line Description Provided by Madigan	Patient Narrative From Study Report	Furberg's Classification Based On One-Line Description	Adjudication by Three Board-Certified Cardiologists Based On Patient Narratives
N49-97-02-071 Patient # US0382-1310	"Chronic obstructive pulmonary disease"[1] [**Note**: Phrase does not appear in patient narrative at all.]	"**Patient No. US0382-1310** (sudden death): [Patient] was a 78 year old male with a history of osteoarthritis, hearing loss, sinus congestion, hypertension and emphysema. The patient was enrolled into the study on 11 September 1997 and randomized to receive ibuprofen 800 mg TID. After 32 days of treatment, the patient called the study coordinator and advised her that he was stopping study medication on his own due to increasing edema in his ankles. He was withdrawn from the study eight days later. The edema subsided an unknown number of days after stopping study medication. Sixteen days following this visit, on November 6, 1997, the patient experienced severe abdominal pain. **While getting into his car to go to the doctor, he collapsed and expired.** The patient had previously been diagnosed with a urinary tract infection and was being treated by his primary physician. No autopsy was performed. Concomitant medications at the Early Termination Visit included nifedipine, metaproterol sulfate and triamcinolone acteonide. The Investigator and the Searle Medical Monitor considered this event to be unrelated to study medication."[2]	Noncardiovascular event[1]	Cardiovascular death[3]

Notes:
[1] Markel Decl., Ex. 198 (Madigan Ex. 20 Spreadsheet).
[2] Markel Reply Decl., Ex. 419 at Clinical Trials 00438894-95 (N49-97-02-071 Study Report) (emphasis added); *see also* Defs.' Br. at 45 n.53 [defining sudden cardiac death].
[3] *See* Markel Reply Decl., Ex. 418 at 3 (Cardiologists Adjudication Combined, PFE ADJUD 00600-604).

Figure 18

Furberg's Testimony on Fatal "Hard CHD" Events in Alzheimer's 001 Conflicts with the Spreadsheet Plaintiffs Attribute to Furberg.

Furberg's "Hard CHD" Events In Alzheimer's 001 – Spreadsheet vs. Deposition			
Patient No.	**Event Description**	**Hard CHD? (Spreadsheet)[1]**	**Hard CHD? (Deposition)[2]**
501	Severe cardiac failure, bilateral pneumonia, pulmonary fibrosis	Yes	No
411	Probably atrial fibrillation	Yes	No
308	Myocardial infarction	Yes	Yes
637	Cardiac pulmonary arrest, secondary to cerebral vascular disease	Yes	Maybe

Notes:
[1] Markel Decl., Ex. 198 (Madigan Ex. 20 Spreadsheet).
[2] *See* Markel Decl., Ex. 8 at 407-09 (Furberg Dep. [regarding patient 637, Furberg called that event "a tricky one" and said he would need to know more before he could count that death as a "Hard CHD" event).